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THE MECHANISM OF PRODUCTION OF BREATH SOUNDS

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MUNICH, GERMANY

Since Baas [1] proposed the theory that vesicular breathing was only modified bronchial breathing, two different opinions have prevailed as to the origin of the breath sounds. According to one theory, the specific vibration of the porous tissue of the lung put in motion through respiration causes vesicular breathing; the second theory, like that of Baas, maintains that the vibrations of the bronchial system alone force their specific frequency on the tissues of the lungs and on the chest wall, respectively, being there either weakened or strengthened, according to the physical conditions of the vibrations of the air and of the conducting tissue of the lung. To the latter process, the laws of the so-called forced vibrations, as first proved by O. Frank,[2] should be applicable. These laws may be of interest:

1. A correct conduction of the sound is possible only if the specific sound and the specific frequency,[3] respectively, of the conductor of sound (for instance, of the tissue of the lung) are of a higher pitch than all the partial tones of the sound to be conducted.

2. If partial tones of the sound to be conducted are higher pitched than the specific sound of the conductor, they will be considerably weakened.

3. If some are lower, they will be conducted correctly.

4. If a partial tone of the sound to be conducted and the specific sound of the conductor attune in their pitch of tone (frequency per second), resonance may result.

If these laws are to be applied to the problem of auscultation, the kind of motion of the tissue of the lung, both air-bearing and solidified, which serves as a conductor of sound, both of the air-bearing tissue

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* From the II Medical Clinic (Friedrich von Müller) of the University of Munich.

1. Baas: Deutsch. Arch. f. klin. Med. **69.**

2. Frank, O.: Ztschr. f. Biol. **53, 56.**

3. The pitch of the proper sound of a body increases with its firmness; it decreases with its size. The pitch and frequency of sound and the frequency per second are proportional.

and of the solidified one must be clear. Furthermore, we should be clear about the origin and the qualities of the vibrations originating in the laryngobronchial system.

The first task leads to the problem of percussion, the mechanism of which has been investigated for many years at our clinic under the guidance of Dr. Friedrich von Müller.[4] We believe that we have finally succeeded in solving this problem experimentally. The mechanism of percussion bears a great resemblance to the beating of a drum. In both cases a thin wall or membrane is struck, behind which is a medium capable of complicating the specific frequency of the wall. Several authorities have already referred to the great importance of the drum theory in connection with the question of percussion, but up to the present time there has been no agreement. Either too great importance was ascribed to the wall for the formation of the tone, leaving to the cavity no function but that of a resonator (the natural philosophers, chiefly, were of this opinion, and recently Bushnell

Fig. 1.—Specific vibrations of the cavity.

expounded this theory [5]); or it was thought that only the cavity is of importance for the pitch of tone, while the membrane only renders the transmission of the waves of the sound to the atmosphere more or less difficult. The majority of physicians believed the latter.

In order to solve the problem a model was required, the parts of which could be observed both singly and in combination. For this purpose, I constructed a cube-shaped wooden box with strong walls and open on one side; this side could be closed with a wooden plate replacing the membrane of the drum. By means of this box the problem was solved graphically.

At first the specific vibrations of the plate and of the cavity were registered separately, whereby typical curves were produced by both (Figs. 1 and 2). Then the vibrations of the closed system (cavity plus

4. Müller, Frederic von: Verhandl. d. d. Kongr. f. inn. Med. 1911; Ztschr. f. ärztl. Fortbild., 1912. Lelling, T.: Arch. f. klin. Med. **90**. Edens and Ewald: Arch. f. klin. Med. **123**. Martini, P.: Arch. f. klin. Med. **139**.

5. Bushnell, George E.: The Mode of Production of the So-Called Vesicular Murmur of Respiration, J. A. M. A. **77**:2104 (Dec. 31) 1921.

plate) were registered (Fig. 3). The plate did not predominate over the cavity nor the cavity over the plate, but the single parts of the entire system forced their specific vibrations reciprocally on each other. By means of such drumlike systems the specific vibrations of one predominating system are not forced on the other; the one does not serve as a resonator to the other, but the specific vibrations of both parts are superimposed equally one upon the other.

There is no doubt that the mechanism of the pneumothorax resembles closely that of the model just described. But this is not the case in the same degree under other pathologic and under normal conditions. Normal conditions may be imitated by filling the wooden box

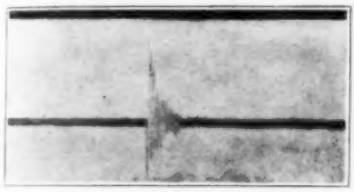

Figure 2

Figure 4

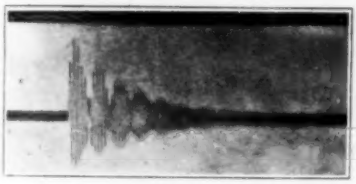

Figure 3

Figure 5

Fig. 2.—Specific vibrations of the plate.

Fig. 3.—Vibrations of the cavity and plate in combination.

Fig. 4.—Vibrations registered by model when normal conditions were imitated.

Fig. 5.—Vibrations shown when model approaches pathologic conditions. Registration shows only vibration of wall; the vibration of the contents has completely disappeared.

with a porous tissue, such as cellulose. When we did this, two separate vibrations were distinctly registered (Fig. 4).

The model approaches the pathologic conditions if filled with moist cellulose, thus corresponding to massive consolidation. In this case, the registration shows only the vibration of the wall, while the vibration of the contents has completely disappeared (Fig. 5). The mass of the contents being greatly increased, its sensibility is consequently much diminished, so that there can no longer be periodical vibrations.

There is no doubt that on percussion of the chest the wall and the contents are intimately associated. Under normal conditions, the vibrations of the wall will dominate over the vibrations of the contents still less than is the case with our model. Indeed, by the graphic registration of the human tone of percussion, only the specific vibrations of the contents could be registered, never those of the wall. This arose to some extent from the insufficiency of the method, but chiefly because of the minimal energy of the high tones of the chest wall. It was only in consequence of the exceptional and peculiarly partial conditions of sensibility of our ear that they often predominated so clearly in the subjective character of the sound.

With the help of graphic registration, we found over the chest of adults a fundamental note between G and C (from ninety-five up to 130 vibrations a second) (Fig. 6).

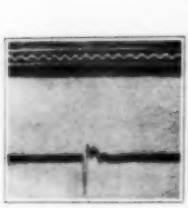

Figure 6

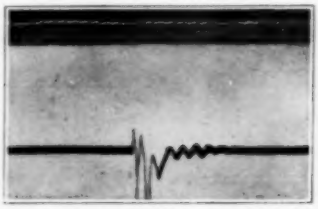

Figure 7

Figure 8

Fig. 6.—Vibrations registered over the chest of adults.

Fig. 7.—Percussion of exenterated lungs when percussed by pleximeter.

Fig. 8.—Percussion tone of solidified lung.

We found the note of percussion of the exenterated lungs to be of exactly the same pitch (Fig. 7) when percussed by means of the pleximeter.

Therefore, I am strongly inclined to contradict Bushnell,[5] when he says "that the sound of percussion, as it reaches the lung, contains the fundamental note," and that it is due to the resonance of the lung of this specific tone of the chest wall, which corresponds to its specific tone. The experiments with our model showed that the specific vibrations of the wall and of the cavity of the box, which are coupled with one another, are simply superimposed on each other. On percussion the same fundamental note was found, whether the lung is percussed directly or by way of the chest wall. This can signify only that the chest wall has little influence on the pitch of the vibrations of the lung and that the vibrations of the contents of the thorax are pure specific vibrations from the beginning, which have their own existence apart

from the vibrations of the wall. Finally, I registered also the note of percussion of the thorax with completely solidified lung (Fig. 8).

In accordance with the experience obtained by filling the wooden model with moist cellulose, no sound of the lung is produced in this case. The completely solidified lung is mute, and what we hear above it on percussion is nothing but vibration of the chest wall. The specific frequency of the solidified lung cannot, therefore, be decided in this manner. So much for the physical conditions of the tissue of the lung, so far as percussion can give any information.

In auscultation, the solid part of the tissue of the lung is to be taken into consideration as a conductor of sound under normal conditions as well as in consolidation. The question is, Is this also to be considered in the origin of sound? For the solidified tissue we may promptly answer in the negative, because it will be just as mute as on percussion. For the air-bearing tissue we must, for the present, leave the question unanswered.

Now we must ask ourselves whether the air does not also come into consideration as a conductor of sound in the much ramified bronchial system of those portions of the lung that are chiefly solid, as mentioned above, or whether it is of importance only as a source of sound. The reply to this question depends on the explanation of the origin of the laryngobronchial breath sounds. I have fully explained in another journal [6] the reason why I do not believe that the vocal cords are of any importance for the origin of this sound, as Geigel has brought forward and Bushnell [5] has again affirmed. After the elimination of the vocal cords through entire paralysis or through a tracheoscope, the breath sounds show hardly any change. This result seems to me to be of much more importance than Bushnell attaches to it. Where else should the bronchial breathing originate after the elimination of the vocal cords through a smooth tube, such as the tracheoscope, if not in the tracheobronchial ramifications? And why should this mode of origin suddenly lose its value, when the tracheoscope, by the introduction of which these vibrations were not affected, is again taken away? That is what we should have to suppose if the sounds—well audible while the tracheoscope was introduced—were no longer audible without the tracheoscope with wide-open throttle, as stated by Bushnell. With wide gaping vocal cords I also always hear breath sounds over the trachea as well as over the lung when the respiration is rapid enough. I do not think that the glottis has an essential part in originating the bronchial breathing, but in my opinion this sound definitely arises from the edges and corners of the bifurcations of the trachea and bronchi.

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6. Martini: Deutsch. Arch. f. klin. Med. **139.**

The larynx is therefore not the origin of the tone whence the sound vibrations are conducted to the periphery of the lung, but the whole tracheobronchial system down to the smaller bronchi is to be looked on as the origin. Under what conditions will this original sound, the specific sound of the air-filled bronchial tree, be clearly audible? Can we auscultate it unaltered? Of what kind of vibrations does it consist? In any event, we can be certain of observing the specific note of the bronchial system by itself, that is, without the addition of other sounds, only when the elimination of specific vibrations of the solid tissue of the lung is guaranteed. This is the case in massive consolidation, when, as can be shown, the solid tissue of the lung is completely mute. The site for auscultation of the vibrations taking place in this bronchial system has to be connected with a bronchus in solidified tissue by a correctly conducting tissue. The best way to ascertain the degree of capacity of a body is to observe by objective registration, if possible,

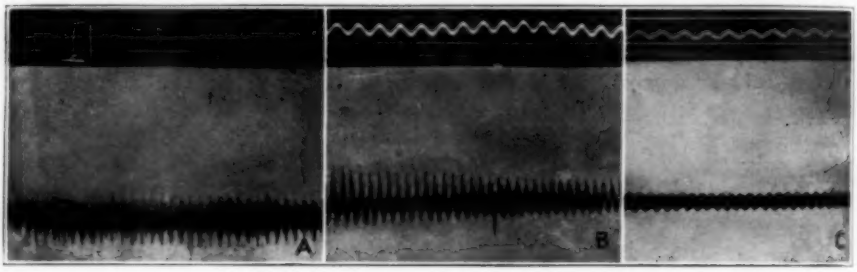

Fig. 9.—Registration of vowels and word sounds made by patients with massive consolidation of lungs into a registering apparatus, *A*; also sounds coming from a solidified lung, *B*; from a normal lung, *C*.

how it modifies known tones and sounds in their passage through it. We made patients with massive consolidation speak vowels and words into a registering apparatus (Fig. 9*a*) and, in addition, we registered the same sounds coming from the solidified (Fig. 9*b*) as well as from the normal lung (Fig. 9*c*). The results were curves such as we see in Figure 9*c*.

The figures show that the vowel "A", in passing through the lung, retains very well its characteristic high overtone of ca-1,000 vibrations a second, while it loses it completely when passing through the air-bearing lung. If, accordingly, the solidified lung is still a good conductor of tones of 1,000 vibrations a second, it will also be able to conduct correctly the specific vibrations of the bronchial system. Thus one hears through a solidified lung, which is laid on the trachea, the voice as well as the tracheal breathing, including their high overtones.

According to Bushnell, the predomination of the high overtones of the bronchial breathing can only be explained on a two-fold supposition. First, Bushnell supposes that in bronchial breathing the bronchi, but chiefly the mouth and the nasopharynx, serve as resonators. This I must contradict; there is not reason why resonance should only be produced in these cavities in consolidations and not in normal conditions. In an earlier publication I have explained why I cannot also acknowledge resonance in the smaller bronchi as the original cause of the bronchial breathing, as Sahli supposes it to be. And still less can it be conceded that, "in massive consolidations of any kind, the deep and medium-pitched tones are suppressed," or, in other words, that the solidified lung cannot give covibrations with the deep tones of the laryngeal sounds, as supposed by Bushnell. The well founded laws of forced vibrations are in absolute opposition to this, as has been our experience, telling us that even tones as deep as the low c (128 vibrations a second), which lie in the lower limit of the human voice, are better propagated through a solidified (infiltrated) lung (Fig. 10*a*), than through an

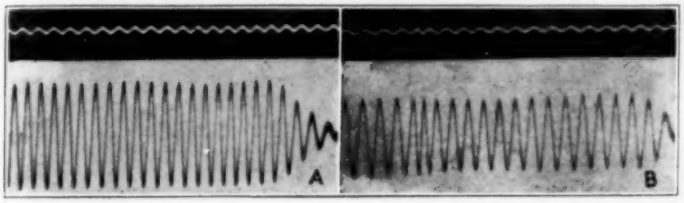

Fig. 10.—Registration of low tones propagated *a* through a solidified lung; *b*, through an air-bearing lung.

air bearing (normal) one (Fig. 10*b*). The bronchial breathing which is audible over solidified tissue, may rightly be considered, as a correctly propagated specific vibration of the air of the bronchial system.

Some time ago, by means of resonators, Dr. Müller estimated the pitch of the bronchial breathing between d^2 and d^3. With the same method, I found an upper limit of c^3 (about 1,000 vibrations a second) and a lower one of d^2 to e^1. In another paper,[7] I have stated why the results which are obtained through resonators can claim but limited validity. We tried, therefore, to register the bronchial breathing objectively from the chest wall and found pitches from e^1 to d^2 and from 300 to 500 vibrations a second, respectively, never lower ones. The periods were always regular, which was to be expected on account of the characteristic, almost musical sound. The conformity with the lower limit of reach of the bronchial breathing which was established by means of the resonators, is evident (Fig. 11).

7. Deutsch. Arch. f. klin. Med. **139**:265.

As to the overtones, which are decisive for the harsh "bronchial" character of the bronchial breathing, the curves gave no evidence, because of the probability that the absolute intensity of the overtones was again very small, much smaller than might have been supposed judging by the subjective acoustic impression.

Concerning vesicular breathing, Bushnell asserts that the physiologic (normal) breathing is only modified laryngeal breathing. I have attempted to prove that the latter is identical with bronchial breathing. We know now its pitch of tone—its fundamental tone reaches at the utmost to e^1 (300 vibrations a second) and lower. We are also sufficiently informed about the specific frequency of the conductor of sound, in this case that of the air-bearing tissue of the lung. With regard to the height of pitch, it will coincide with the established pitch of tone obtained on percussion of the normal lung, consequently, in normal adults, it will lie between A and c (about 100 and 130 vibrations a second). Recently I have been able to define graphically the maxi-

Fig. 11.—Bronchial Breathing.

mum resonance of the lung. On the whole, it was found (working with men only, women's voices being too high-pitched) that the maximum always lay in the pitch of the sound of percussion (Fig. 10*a*). Its quality as a specific tone of the lung was thereby newly affirmed. Also the frequency (pitch of tone) of the specific tone of the bronchi (c^1 to $d^2 = 300$ to 550 vibrations a second) was higher in each case than the specific frequency of the air-bearing, sound-conducting lung. In consequence of this proportion—according to the laws mentioned in the foregoing all specific vibrations of the system of the bronchi would be weakened while passing through the normal lung, the highest would even be extinguished entirely. A decreasing and relative deepening of the breath sounds would follow. In reality this is observed when auscultating the trachea through an air-bearing lung. This explanation is not sufficient for the normal vesicular breathing heard over the human thorax: it will be eliminated by establishing the absolute pitch of tone of the vesicular breathing.

This also was shown graphically (Fig. 12). Its vibrations are much more irregular than those of bronchial breathing; the fundamental frequency fluctuates incessantly between 100 and 200 vibrations a second, which is not astonishing because of its noisy character. Thus vesicular breathing is not only relatively, but absolutely, deeper than bronchial breathing. While these observations cannot be in accord with the supposition of entirely forced vibrations and of resonance, respectively, they leave no doubt that, besides the vibrations of the bronchial system, another factor is also of great importance in originating the inspiratory breath sound which is audible over the air-bearing lung. Only the specific vibrations of the tissue of the lung can be taken into consideration as such. Bushnell has hinted at the affinity between vesicular breathing and the normal note of percussion. He thinks that in either case the same resonator responds with its specific tone, in one case to the vibrations of the bronchial system, in the other to the vibrations of the chest wall. There is no doubt that an affinity exists between the two; but we consider the rôle of the lung in the origin of

Fig. 12.—Vesicular breathing.

the percussion-sound and vesicular breathing more important than that of a resonator. We think that the percussion sound corresponds to the sound of a string which has been struck, while we might compare the vesicular murmur to the sound produced by a suddenly strained string. Both tones of the string are different in their color of sound, but their fundamental frequency is of the same pitch. We could assume the same of the suddenly distended and of the percussed lung, and indeed we have found that their pitches agree to a considerable degree. The pitch of the percussed normal lung lies between G and c and even the deepest partial tones, which are contained in the vesicular murmur, reach as far down as the deep G. This conformity of the fundamental frequency makes it probable that percussion and inspiratory tension are but two different methods of bringing the lung out of its equilibrium. The lung endeavors to recover this state of equilibrium, around which it vibrates periodically and with the same fundamental frequency, just as a violin string when struck and when suddenly strained gives different colors of sound, but the same fundamental tone.

SUMMARY

Just as on percussing the air-containing lung, the specific sounds of the two mutually dependent and connected systems—chest wall and lung—determine the percussion sound, so the breath sound over the air-containing lung is composed of two specific sounds: that of the bronchial system and that of the air-containing lung tissue.

Only the sound of the chest wall is heard on percussion over a massively infiltrated lung; the lung itself remains mute. The specific sound of the infiltrated tissue has no part in bronchial breathing obtained over an infiltrated lung. Pathologic bronchial breathing is merely the expression of correctly transmitted vibrations.

During respiration the air in the bronchi is caused to vibrate in the form of split and cut sounds. The glottis is not necessary for this purpose.

The graphic registration of the "lung traveling voice" shows the great importance of the laws of the so-called forced vibrations in the problem of auscultation.

SENSITIZATION TESTS WITH DIGESTIVE PRODUCTS OF PROTEIN *

I. CHANDLER WALKER, M.D., ARTHUR S. WETMORE
AND
JUNE ADKINSON, A.M.
BOSTON

That sensitization to proteins occurs is well established. The only evidence so far produced is that it is the undigested protein that sensitizes and causes symptoms. Frequently, one meets with conditions the symptoms of which would seem to be due to protein sensitization, even though the protein tests are negative. For this reason it seemed to be advisable to try sensitization tests with the decomposition products of proteins in order to determine whether or not they might sensitize and cause anaphylactic symptoms when the whole protein failed to do so. The present work, however, would seem to show that the decomposition products do not sensitize human beings and do not play a part in human anaphylaxis.

We first attempted to digest egg white with normal human duodenal contents in order to simulate as near as possible normal digestion, but this experiment was a failure because of reasons noted below.

DIGESTION OF EGG WHITE WITH HUMAN DUODENAL CONTENTS

The whites of a dozen hard boiled eggs were pressed through a potato ricer and then placed in a 2 liter flask with 1,500 c.c. of water. The contents were acidified with hydrochloric acid to approximately tenth normal; then 100 c.c. of fresh pig stomach extract was added and the mixture incubated at 37 C. until the egg white was completely liquefied. Ten c.c. of this liquefied egg white was titrated with sodium carbonate, and then enough sodium carbonate was added to make the entire liquefied egg white approximately tenth normal alkaline. To this were added 100 c.c. of normal human duodenal contents, obtained by a duodenal tube, and the mixture was incubated two days at 37 C. At the end of this time a slightly modified protein was shown by the Biuret test. Bacterial action was more pronounced than enzyme action; in fact, the enzyme had lost most of its activity. The foregoing process was repeated on liquefied egg white in a neutral medium rather than in a tenth normal alkaline medium, without obtaining better results; that is, the egg was no more changed than it was when digested in the alkaline medium.

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* From the Medical Clinic of the Peter Bent Brigham Hospital. The expense of this investigation was defrayed by the Surdna Foundation of New York.

Since it was thought probable that natural digestion was carried on with a greater dilution of protein than that we had used (our egg being very concentrated), we tried a dilute solution of peptonized egg white. After three days of incubation with 150 c.c. of duodenal contents, the biuret reaction showed a light pink, showing that digestion had progressed further than it had with the concentrated egg white. A biuret-free stage, however, could not be reached without having present a considerable amount of bacteria which were probably due to contamination of the duodenal contents, since the liquefied egg and containers had been sterilized.

By further experimentation, we found that duodenal contents would completely digest a weak solution of protein, provided the duodenal contents contained sufficient natural buffer. We did not know, however, how much of the digestion was due to bacteria and how much was due to enzyme activity.

Therefore, since too dilute a solution of protein had to be used in the digestion by human duodenal contents, and furthermore since the duodenal contents contained bacteria which probably are not present in a person and which played some part in digestion although we could not tell of how much import they were, another method of digesting proteins was employed—artificial digestion.

ARTIFICIAL DIGESTION

The common food proteins, namely, egg, wheat globulin, milk, beef, lamb and pork, which often cause asthma, eczema and perennial hayfever, and to which such patients are sensitized, were selected for the digestion experiments. These proteins were digested in the following manner:

Extraction of Enzymes from Fresh Glands.—The fresh pig stomach extract referred to in the digestion of the proteins was obtained as follows: The glands were removed from the wall of fresh pig's stomach, washed in cold water for a few minutes, cut up finely and allowed to soak over night in twentieth normal hydrochloric acid containing 1 per cent. of glycerin; 250 c.c. of acidulated glycerin solution were used for each stomach gland. The mixture was strained through cheese cloth and then through cotton; the filtrate should be almost clear. The filtrate which contained the enzyme pepsin was preserved with 1 c.c. of a 5 per cent. alcoholic thymol solution and kept in the icebox.

The pancreas extract was obtained by chopping finely fresh pig pancreas and allowing it to stand over night in 200 c.c. of one hundredth normal hydrochloric acid, to which was added 1 c.c. of glycerin. The following day the mixture was strained through cheese cloth and then through cotton. The extract was preserved by addition of 1 c.c. of a 5 per cent. alcoholic thymol solution and kept on ice.

The intestine extract was prepared from fresh pig in the following manner: Twenty-five feet of intestines beginning at the pylorus were washed by running cold water through; then the intestine was chopped finely and allowed to soak over night in 250 c.c. of twentieth normal hydrochloric acid which contained 1 per cent. of glycerin. The following day the mixture was strained through cheese cloth, then through cotton and preserved by the addition of 1 c.c. of a 5 per cent. alcoholic thymol solution and kept on ice.

Digestion of Egg White.—The whites of a dozen hard boiled eggs were pressed through a potato ricer and placed in a 2 liter flask with 1,500 c.c. of 0.1 per cent. hydrochloric acid, and a small amount (usually 4 c.c.) of alcoholic thymol (5 gm. thymol dissolved in 100 c.c. of 95 per cent. alcohol) was added to prevent bacterial growth. To the contents of the flask were added 75 c.c. of fresh pig stomach extract and incubated over night in a water bath at 40 C. Then 75 c.c. more of pig stomach extract were added and incubated another twenty-four hours. At the end of this forty-eight hours' digestion, 300 c.c. were removed and called fraction No. 1. The remaining contents of the flask from which No. 1 was withdrawn were made slightly alkaline (refer Table 1) to litmus by the addition of a saturated solution of sodium carbonate. Then 25 c.c. of pancreas extract and 20 c.c. of intestine extract were added. Incubation was continued for forty-eight hours at 40 C.; at the end of which time 200 c.c. were removed and called fraction No. 2. From now on the process remained the same, namely, at the end of each forty-eight hours of incubation a fraction was withdrawn until a total of five or six fractions were obtained. After withdrawal of each fraction, 25 c.c. of pancreas extract and 20 c.c. of intestine extract were added. Throughout the digestion, after fraction No. 1 had been withdrawn the contents were kept alkaline by the addition of a little sodium carbonate, but not more alkaline than 0.1 normal. Thymol was present throughout to prevent bacterial growth.

A similar experiment was carried on without thymol, thus allowing bacterial growth to take place, with the result that digestion proceeded much more rapidly, and the amino acid stage was reached much more rapidly. Since the bacterial action would complicate the enzyme and foreign substances other than those due to simple enzyme activity would be formed, thymol was added as noted above.

Digestion of Beef, Pork and Lamb.—One and one half pounds (680 gm.) of finely chopped lean meat were placed in a 2 liter flask with 1,500 c.c. water and sterilized in the autoclave at 15 pounds' (7 kg.) pressure for twenty minutes. The mixture was then cooled to room temperature, made slightly acid to litmus with hydrochloric acid, and the same process as described for egg white was then carried out, except that only 2 c.c. of thymol solution were added.

Digestion of Milk.—In a 2 liter flask were placed 1,500 c.c. of skimmed milk, to which were added 1 c.c. of hydrochloric acid and 2 c.c. of thymol. From now on the process was identical with that described for egg white.

Preparation and Digestion of Wheat Globulin.—Whole wheat flour (300 gm.) was placed in a large container and extracted twice with 4 liters of 10 per cent. sodium chlorid. The mixture was stirred until the flour and salt were thoroughly mixed and is allowed to stand three days. In a similar manner the wheat flour was extracted a second time with 4 liters of 10 per cent. sodium chlorid, thoroughly mixed and allowed to stand three days. The flour settled to the bottom and the pinkish supernatant fluid was siphoned off. From the supernatant fluid obtained from both extractions together, the globulin was precipitated by saturation with sodium chlorid. The precipitated globulin settled to the bottom after several days so that the supernatant fluid could be decanted and the contents at the bottom of the flask centrifuged at high speed, thus separating out the globulin. The globulin was then placed in a 2 liter flask to which 1,500 c.c. of water were added and sufficient hydrochloric acid to make the mixture slightly acid to litmus. Three cubic centimeters of thymol solution were added, and from then on the process was the same as described for egg white.

FURTHER TREATMENT OF DIGESTIVE FRACTIONS

The various fractions of digestion were treated as follows: In order to have them in a dry powdered form, each fraction was evaporated slowly on a water bath until an almost dry, sticky residue was obtained. Then 50 c.c. of 95 per cent. alcohol were added and thoroughly mixed with the sticky residue and again evaporated. This process was repeated four times to remove water. The residue was finally dried in a vacuum desiccator containing sulphuric acid and powdered with a mortar and pestle. The powder is very hydroscopic and needs to be kept in air tight bottles. With wheat globulin the fractions were evaporated to dryness on a water bath placed in front of an electric fan which kept the air over the evaporating dish in circulation. To the dry residue, 100 c.c. of absolute alcohol were added, and the mixture was allowed to stand at room temperature for thirty minutes. Then the mixture was stirred, filtered, pressed through a filter paper to express as much alcohol as possible and finally dried in a sulphuric acid vacuum desiccator. When dry the substance may be powdered as was done with the other digestive fractions, as already described. With the wheat globulin digestion was carried through five fractions rather than six as was the case with the other food proteins.

Table 1 shows why, after pepsin digestion, the mixture was made alkaline before the addition of trypsin.

The casein used in the table was a solution of 1 gm. casein in 100 c.c. water and 4 c.c. tenth normal sodium hydroxid. The enzyme used consisted of 1 c.c. of pancreas extract (already described) and 1 c.c. intestine extract (already described), diluted with water. Two c.c. of a 25 per cent. metaphosphoric acid solution was used to precipitate the protein. The various tubes containing the ingredients as per table were incubated 30 minutes at 40 C.

The foregoing experiment definitely shows that trypsin has five times more proteolytic activity in a one fifteenth molecular alkaline phosphate solution than it has in a one fifteenth molecular acid phosphate solution. For this reason, in the digestive experiments, the acid reaction after pepsin digestion was changed to an alkaline reaction before the addition of trypsin.

SENSITIZATION TESTS WITH THE DIGESTIVE FRACTIONS

It seemed desirable first to test the digestive fractions on a group of patients who gave positive cutaneous tests with the whole protein;

TABLE 1.—*The Effect of Acid and Alkaline Phosphate on Trypsin*

Tube	Casein	1/15 Molecule Sodium Phosphate	1/15 Molecule Potassium Dihydrogen Phosphate	Dilute Enzyme Solution	Mg. Nitrogen per 100 C.c. of Filtrate
I	5 c.c.	0 c.c.	5 c.c.	1 c.c.	0.4
II	5 c.c.	1 c.c.	4 c.c.	1 c.c.	0.56
III	5 c.c.	2 c.c.	3 c.c.	1 c.c.	1.40
IV	5 c.c.	3 c.c.	2 c.c.	1 c.c.	2.00
V	5 c.c.	4 c.c.	1 c.c.	1 c.c.	3.50
VI	5 c.c.	5 c.c.	0 c.c.	1 c.c.	5.00

in other words, to test known sensitive patients with the digestive fractions. In Table 2 are presented the results of the cutaneous test with both the whole protein and its digestive fractions. For convenience the table is divided into Part A and Part B. The first column of each part shows the patient's diagnosis, the second column contains the patient's initials, the third column shows the particular protein to which the patient is sensitive and also the size of the cutaneous reaction or the degree of sensitiveness of the patient to that protein; for instance, a plus means a wheal at least 0.5 cm. in diameter, a 1 + means a little larger reaction, a 2 + mean a wheal at least 1 cm. in diameter, and so on. The columns headed digestive fractions gives the results with each fraction of the protein to which the patient is sensitive; a ± means a doubtful reaction, 1 — means a more definite reaction than ± but not enough to call a + and a question mark means that there was a slight reddening or irritation which should probably be called negative. In fact, probably all reactions labeled ± or question mark should be called

negative, and those designated 1— probably mean nothing when compared with such definite reactions as were given by the whole protein.

The first five patients in Part A of Table 2 had eczema, the sixth had angioneurotic edema and the remaining twelve had bronchial asthma. It is noted that the majority of the patients reacted positively with the first fraction of digestion, and nearly all of these same patients

TABLE 2.—*Results of Cutaneous Tests with Whole Protein and Its Digestive Fractions*

Diagnosis	Patient	Protein	Digestive Fractions					
			1	2	3	4	5	6
Part A:								
Eczema	F. H.	Globulin... +	±	±	±	±	±	
Eczema	.....	Egg..... 1+	?	?	0	0	±	±
Eczema	G. H. W.	Globulin... +	+	+	+	±	±	
Eczema	C. P.	Globulin... +	1—	±	0	0	0	
		Egg..... +	?	±	?	?	0	1—
Eczema	F. D.	Milk..... 2+	+	+	0	0	0	0
Angioneurotic edema	F.	Globulin... 1+	±	1—	?	?	±	
Asthma	W. J. D.	Globulin... +	1+	1—	1+	±	?	
Asthma	A. C. C.	Pork..... +	1—	±	0	0	0	0
		Lamb..... +	0	?	?	1—	1—	1—
Asthma	J. F. P.	Globulin... 3+	1+	+	1—	1—	1—	
Asthma	M. E. B.	Globulin... 1+	1+	+	±	±	±	
Asthma	C. G. F.	Globulin... 2+	+	+	+	±	±	
Asthma	A. J. A.	Pork..... 1+	0	0	0	±	1—	1—
Asthma	P. K.	Beef..... 1+	±	±	1—	+	+	?
Asthma	F. R.	Globulin... +	+	+	±	±	?	
Asthma	J. L.	Globulin... +	+	+	0	0	0	
Asthma	J. M.	Globulin... 2+	2+	±	±	±	±	
Asthma	W. T. M.	Globulin... 1+	1—	1—	±	±	±	
Asthma	Bar.	Globulin... 1+	+	+	±	0	0	
Part B:								
Eczema	R. J.	Casein..... +	0	0	0	0	0	0
Eczema	G. H. W.	Egg..... +	0	0	0	0	0	0
		Milk..... +	0	0	0	0	0	0
Eczema	F. D.	Egg..... 2+	0	0	0	0	0	0
Angioneurotic edema	F.	Beef..... +	0	0	0	0	0	0
Asthma	A. C. C.	Beef..... +	0	0	0	0	0	0
Asthma	J. R.	Globulin... 2+	0	0	0	0	0	
Asthma	A. O. F.	Egg..... 1+	0	0	0	0	0	0
Asthma	C. A. N.	Pork..... +	0	0	0	0	0	0
		Lamb..... +	0	0	0	0	0	0
Asthma	P. H. F.	Pork..... 1+	±	0	0	0	0	0
Asthma	F. S.	Globulin... 1+	0	?	0	0	0	
Asthma	E. McC.	Egg..... 1+	?	?	?	?	?	?
Asthma	L. S.	Globulin... +	?	?	?	?	?	
		Egg..... +	+	0	0	0	0	0
Asthma	P. K.	Egg..... +	0	0	0	0	0	0
		Globulin... +	+	0	0	0	0	
Asthma	H. F. B.	Pork..... +	1—	0	0	0	?	?
G. I.	Dr. B.	Pork..... +	0	0	0	0	0	0

reacted positively to the second fraction; but in only five instances did the third fraction give a positive reaction; the fourth fraction gave positive reactions in only three instances, and the fifth fraction in four instances; the sixth fraction gave a weak test in three of the seven cases tested. In other words, the first two fractions reacted more nearly like the whole undigested protein, and their positive reactions might well be explained as being due to the presence of the original protein which had not yet been acted on by digestion; in no instance did the first two fractions react more strongly than the original whole

protein, and in only five instances were the tests with the first two fractions as positive as with the whole protein. In the majority of cases, there was a decrease in the positiveness of the reaction as the succeeding fractions were tested. In cases C. P. with egg, A. C. C. with lamb, A. J. A. with pork, and P. K. with beef, the fifth and sixth fraction did react more strongly than the other fractions, but these reactions were less marked than the reactions given by the whole undigested proteins; with only one of these four patients (P. K.) was the reaction given by the fifth or sixth fraction a real positive, and with this case the sixth fraction was negative. Therefore when digestion was most complete and the greatest quantity of amino acids were present in the substance being tested, an occasional weakly positive reaction was given but such reaction was in no instance as large as that given by the undigested protein. From this part of the table it might be concluded that the digestive products of protein probably do not sensitize, or at least when the whole or undigested protein does give a definite positive reaction, its digestive products give less positive reactions, and the more complete the digestion is the less is the reaction given.

In Part B of Table 2 are represented three patients who had eczema, one who had angioneurotic edema, ten who had bronchial asthma and the fifteenth or last patient who had gastro-intestinal cramps and colic. In only three instances did the first fraction of digestion give any reaction, and in only one (P. K.) was the reaction definitely positive. These three reactions might well be due to the presence of undigested protein. In no instances did the other fractions of digestion give any reaction. Therefore this part of the table furnishes strong evidence against sensitization to the digestion products of proteins in those patients who are definitely sensitive to the whole protein.

Since known positive food cases, as shown in this table failed to give positive reactions with the digested products, it would not be expected that patients who failed to be sensitive to the whole protein would be sensitive to the digestive products. A large number of patients who had bronchial asthma and eczema, and who failed to give a positive cutaneous test with whole proteins, were tested with these digestive fractions, and in only two instances were reactions obtained. One, a patient with eczema that reacted slightly to casein, did react more positively to fractions one and two of milk, but failed to react to the other fractions. The other patient also had eczema and did react positively to the first four fractions of wheat globulin, whereas whole wheat globulin and fraction five failed to react. These two cases, however, considering the large number tested, do not change the conclusions already stated, namely, that the digestive products of proteins probably do not sensitize.

ARTIFICIAL DIGESTION WITH BACTERIA

As already stated, the previous digestion experiments were carried on under sterile conditions. Since in the human intestinal tract bacteria are normally present, we allowed bacteria to digest or act on the proteins. As bacteria probably play little or no part in digestion of proteins in the stomach, duodenum and upper intestinal tract, we digested the proteins as previously described up to and including the point where the second fraction was removed; in other words, we allowed the proteins to be acted on by pig stomach extract in the presence of hydrochloric acid for forty-eight hours, then neutralized and allowed pig's pancreas and intestine to act on the proteins for forty-eight hours. The mixture was then sterilized at 15 pounds' pressure for twenty minutes in order to kill the enzymes and stop their activity. This partially digested protein mixture, as shown by the fact that the biuret test showed no true protein to be present, was equally divided into three parts, and each part was placed into a sterile flask. To the contents in each flask were added 2 gm. of lactose and 3 c.c. of glycerin in order to give the bacteria about to be added a more nutrient medium until they might become adapted to growth in the protein digestion mixture. We selected *Bacillus acidophilous*, *Bacillus coli-communis* and *Bacillus proteus* for continuing the digestion, because the former is a normal inhabitant of the infant's gastro-intestinal tract, and in the adult its administration seems to be efficacious in the relief of some conditions, more especially in the relief of obstinate diarrhea and digestive disorders. The latter two organisms are normal inhabitants of the gastro-intestinal tract of older persons, and in addition *Bacillus coli-communis* does decompose proteins, or is proteolytic.

One flask was inoculated with each of the foregoing organisms and incubated for four days at 37 C. At the end of this time, the contents of each flask were examined to make sure that the bacteria were still alive. One hundred c.c. were withdrawn from each flask, sterilized and evaporated to 8 c.c. under vacuum at a temperature not above 50 C. These samples were called fraction No. 1. The remaining contents of each flask were incubated another period of forty-eight hours, after which the contents were examined to demonstrate that the bacteria were still living; then another 100 c.c. were withdrawn and sterilized and evaporated as before. This was called fraction No. 2. In a similar manner, fractions No. 3, No. 4 and No. 5 were obtained.

All fractions were then heated for one hour at 65 C., after which they were transferred to sterile bottles and kept on ice for future use in testing patients.

The evaporation of each 100 c.c. withdrawn was carried out in the following manner. Into flasks with two side arms were placed the 100 c.c. of digestion mixture; the flask was suspended in a water bath so

that the delivery tube (one side arm) was at an angle of 45 degrees, and it was inserted into the neck of another or receiving flask which was held at the proper angle by means of a clamp. The other or free side arm was used for applying the vacuum. A manometer placed in the vacuum line helped to control the temperature by applying approximately the same degree of vacuum from day to day; a vacuum of 480 mm. of mercury was used.

In a similar manner wheat globulin, milk and beef were treated, and from each five fractions were obtained for use in testing patients.

A series of twenty-five patients who were sensitive to one or more of the whole proteins were tested with all of the bacterial fractions obtained from each protein. A table illustrative of these tests would be too long and too complex to be of any advantage; therefore a general summary of such a table is given. About one third of the patients failed to give a positive reaction with any of the fractions and another third gave positive reactions with most of the fractions. However, as many patients who were negative to the whole protein gave a positive reaction with its fractions as did those who gave positive reactions with the whole protein. In other words, the fractions gave positive reactions irrespective of whether the whole protein did or did not react positively. In the remaining third of the series, some of the fractions reacted positively, but the majority of the fractions failed to react; more often, those who would be expected to react positively failed to do so, and vice versa. The fractions obtained from the digestion of all proteins with *Bacillus coli-communis* gave the largest number of positive reactions, and the fractions obtained from the digestion of all four proteins by *Bacillus acidophilus* gave the smallest number of positive reactions. These results could not be correlated with the positive tests with the whole protein. Furthermore, in no instance was a two plus reaction obtained, and often a doubtful or ± reaction was given. From these varying and erratic results, we felt that we were getting no true anaphylactic reactions, but instead that the fractions were irritative to the skin and nonspecific reactions were being obtained due to irritation of the fractions.

In order to determine whether the fractions were irritative to the skin or not, thereby giving false reactions, a series of twenty-five patients who had various conditions and whom we had no reason to believe were sensitive to proteins and in whom the whole protein gave negative reactions, were tested with all of the fractions obtained from the four proteins that were digested with the bacteria. In other words, the foregoing experiment was duplicated, using known negative cases. In this series of cases, one third gave negative reactions with all of the fractions of all four proteins. Four other cases gave positive reactions with beef digested with *Bacilli coli-communis* alone but were negative to all of the other fractions of beef as well as to milk, globulin and

egg. Three other patients gave positive reactions with beef and milk coli communis fractions but negative reactions with all other fractions. The remaining cases reacted too irregularly to warrant description. The beef and milk *Bacilli coli-communis* fractions reacted most frequently and all *Bacillus acidophilus* fractions reacted least often (in only five patients did these fractions give any reaction). No patient reacted to every fraction; in only three instances was a two plus reaction obtained, and frequently a doubtful or ± reaction was given. This experiment duplicated closely the former one; therefore similar erratic results were obtained with both known sensitive and known nonsensitive patients. It would therefore seem that the fractions were irritating to the skin and that some fractions were more frequently irritating than others.

Although a definite interpretation cannot be made from the results of the two foregoing experiments, we can definitely state that the evidence is against sensitization of persons to the digestion products of proteins obtained through the action of the usual intestinal bacteria.

The suspected irritative property of the bacterial fractions we attempted to remove by dialysis; since some fractions were very acid and others very alkaline, it was possible that the increased acidity or alkalinity might be the source of irritation; furthermore the black coloring matter present in the fraction might be irritable. All fractions were dialyzed until they were practically neutral, and all coloring matter in the majority of the fractions had disappeared.

Twenty-five patients with miscellaneous conditions were tested with the dialyzed fractions, with the following results: Only one patient gave negative reactions with all of the fractions, whereas previous to dialysis eight patients reacted negatively. Three other patients gave only doubtful tests with the fractions of one protein, and no patient reacted to all of the fractions of all proteins. No positive reactions were given by the fractions of egg digested by *Bacillus acidophilus* or by *Bacillus proteus*, and only one patient gave positive reactions with egg digested by *Bacillus coli-communis;* therefore dialysis did diminish the number of positive reactions obtained by egg bacterial digestion. With milk, however, a larger number of positive reactions were obtained after dialysis than was the case before dialysis, and with the globulin fraction the results were practically the same both before and after dialysis. With beef *Bacillus acidophilus* and *Bacillus proteus* fractions gave similar results both before and after dialysis, whereas *Bacillus coli-communis* fractions gave six less positive reactions after dialysis than they did before dialysis but even here the fifteen positive reactions were far too many for supposedly negative patients. In general, dialysis seemed to render some fractions more irritable, other fractions less irritable and the remaining fractions remained unchanged. Therefore, neither the removal of coloring matter nor the change in reaction, either acid or alkaline to neutrality, lessened our difficulty of false reactions

or diminished to any appreciable extent the irritability of the fractions. For these reasons further experimentation with these bacterial fractions was discontinued.

Although further consideration of the bacterial digestive products seemed to be unwarranted, the testing of eczema patients with the sterile fraction was continued until a series of fifty persons was completed. The results verified the conclusions already stated. Therefore, contrary to our expectations, eczema patients are not sensitive to the decomposition products of proteins, and we have no evidence that the partially or completely digested protein causes eczema. When proteins cause eczema, as they often do, the whole or undigested protein is the causative agent.

SUMMARY

We attempted to digest proteins with normal human duodenal contents but failed because the action of the bacteria which was present in the duodenal contents was more pronounced than the activity of the enzymes; furthermore, too dilute a solution of protein had to be used to make the results practical.

Artificial sterile digestion using pig's stomach, pig's pancreas and pig's intestine extracts was successful. Since egg white, beef, pork, lamb, milk and wheat globulin are the usual proteins to which patients with asthma and eczema are sensitive, these proteins were selected for digestion. Every forty-eight hours a fraction of digestion was removed, namely, fraction No. 1 after forty-eight hours in the presence of stomach extract and hydrochloric acid, fraction No. 2 after forty-eight hours in the presence of pancreas and intestine extracts in an alkaline medium, and fraction Nos. 3, 4, 5 and 6 each after forty-eight hours' successive intervals. The proteins soon lost their identity as such, and the amino acid stage was gradually reached until in the last two fractions only amino acids were present. The various fractions were treated until a dry, hydroscopic powder was obtained, and with these cutaneous tests were made.

In Table 2 are presented the results of tests with these fractions on known sensitive patients. The first two fractions reacted positively in a number of cases; but it is not certain that sufficient undigested protein was present to account for these positive tests. The later fractions usually reacted only slightly positively or not at all. This table would seem to show that digestive products do not sensitize, even though the whole protein from which the fraction was derived does react positively. A series of patients who failed to react positively to the whole protein reacted likewise negatively to the digestive products.

Artificial digestion was then carried out in the presence of bacteria as follows: After digestion through the second fraction was completed, the mixtures were sterilized, divided into three parts and to each portion was added respectively, *Bacillus coli-communis, Bacillus proteus*

and *Bacillus acodophilus*. After the addition of these bacteria, fractions were withdrawn each forty-eight hours until a total of five fractions were obtained, and with these the patients were tested.

In a series of known negative miscellaneous cases, these bacterial fractions gave too numerous and too erratic results, which were attributed to the possibility that the fractions were very irritable to the skin. Since some of the fractions were quite acid and others were quite alkaline and all contained a dark coloring matter, the fractions were dialyzed until all were approximately neutral and practically free from coloring matter. The dialyzing, however, seemed to make little difference in the results of tests on known negative patients; therefore further experimentation with the bacterial fractions was discontinued.

A series of patients with eczema were then tested with the dry fractions obtained by sterile digestion, with the result that the patients who failed to give positive tests with the whole protein likewise gave negative tests with their digestive products. Therefore this work would seem to show that there was no advantage in testing patients with the digestive fractions of proteins and that probably digestive products do not sensitize.

CONCLUSIONS

When whole proteins give a strong reaction, the amino acid of the corresponding protein does not. The suspected substance which might react on the anaphylactic patients was thought to lie somewhere between the true proteins and the amino acids, but the results obtained in this work tend to show that the further one gets away from the true protein the less the reaction. This is borne out clinically by the fact that the known protein anaphylactic cases react quickly after the ingestion of the protein, to which they are sensitive.

It seems reasonable to assume that anaphylaxis does not take place until the offending protein gets into the blood; therefore, there must be a slight assimilation of an almost true protein or slightly altered protein which, considering the short space of time between the ingestion of the protein and the anaphylactic reaction, could be no more than peptonized.

Peptones and proteoses prepared by the simple hydrolysis of proteins may cause sensitization as has already been shown.[1]

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THE VITAL CAPACITY OF THE CHINESE: AN OCCUPATIONAL STUDY *

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The use of the spirometer as a clinical instrument of precision, introduced by Jonathan Hutchinson in 1846, has been brought into more general use through the more recent researches of Peabody,[1] Wentworth,[2] Dreyer,[3] West,[4] Wilson, Edwards,[5] Lundsgaard, Van Slyke,[6] Hewlett and Jackson [7] and others. The normal standards suggested by Hutchinson have been modified, and the relation to the body measurements of height, weight, body surface, chest volume and circumference have been determined for various groups of persons.

The value of spirometry as an index to the patient's clinical condition has already been demonstrated in cardiac [8] and pulmonary disease.[9] Conditions necessary for the more general adoption of this method are: (1) a simple technic; (2) accurate normal standards with knowledge of the normal range, and (3) knowledge of the factors influencing vital capacity. The first is fairly standardized, and although the apparatus is cumbersome and not easily portable, it is easy to manipulate and accurate, provided the cooperation of the patient can be obtained. Normal standards for men, women and children have been investigated, and figures representing the ratios of vital capacity to body surface

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and to height, in terms of liters per square meter of surface and in cubic centimeters per centimeter of height, have been adopted. West,[4] after an analysis of eighty-five medical students and forty-four nurses, decided on 2.5 liters per square meter body surface for men and 2 liters for women as a normal. A ratio of 25 c.c. per centimeter of height for men and 20 c.c. for women was also proposed; men with an athletic history were given 2.8 and 29 as surface and height ratios, respectively. Wilson and Edwards,[5] from a study of 362 school children in New York City, adopted standards for children of 1.93 for surface and 15.5 for height ratios.

Clinical studies and reports are leading to a clearer understanding of the importance of the various factors which affect vital capacity, such as diseases of the heart and lungs, general physical condition, body strength and weakness,[10] and the effect of age, race, athletics, posture,[11] social environment, etc. All are necessary for a proper evaluation of results.

METHOD

In taking vital capacity measurements on Chinese during routine physical examination of students of the College of Yale in China and city schools, also of patients in the Hunan-Yale Hospital, it was found that the vital capacity of the Chinese fell considerably below the standards adopted for Americans. The following investigation was therefore undertaken to determine a normal standard for the Chinese, and incidentally, to study the effect of various occupations on the vital capacity.

The instrument used was a water spirometer of 6½ liters' capacity. This was copied by a local brass smith from a Narragansett Machine Company model owned by the local Y. M. C. A. Our machine was calibrated by the physics department of the premedical department, and, in operation, has checked accurately with the original.

The procedure in each case involved a careful explanation and demonstration of the method. Care was taken to see that the person took his deepest inspiration. Maximum efforts were stimulated by the competition which always developed when a number were being tested. Two to five attempts were recorded, and the highest taken as the vital capacity. Unsatisfactory cases were discarded. Routine physical examinations were not attempted, although men with gross defects

10. Peabody, F. W., and Sturgis, C. C.: Clinical Studies of the Respiration. VII. The Effect of General Weakness and Fatigue on the Vital Capacity of the Lungs, Arch. Int. Med. **28**:501 (Nov.) 1921.

11. Christie, C. D., and Argyl, J. B.: The Estimation of Normal Vital Capacity with Especial Reference to the Effect of Posture, Arch. Int. Med. **30**:34 (July) 1922.

were not accepted. All were doing their daily work and were in apparent good health. Weights were taken in pounds on the hospital balance scales and on a portable spring scale which had been checked with the balance type, and later changed to kilograms. Measurements were taken with clothing on. As the amount of clothing varies considerably in different classes of persons and in different seasons of the year, an average costume for each group was weighed and correction was made at the time of calculation. As some were barefoot, a correction was made for those wearing shoes. Body surface was determined from the height and weight by use of the DuBois [12] chart. Ratios to body surface and to height were calculated and the results tabulated.

RESULTS OF INVESTIGATION

Records of over 600 were obtained, representing many types, ages and occupations; of these, only 500, in ten groups, were taken for analysis. The results can be best appreciated by a brief discussion of each group.

Soldier Group.—In this group were ninety-seven soldiers, 18 to 40 years of age, from the Changsha military barracks. They probably represent the average soldier of the Hunan provincial troops. Records were taken after a daily drill. Deductions of 4 pounds (2 kg.) for weight of uniform and 1 cm. for height were made. The average for the group was 1.89 for surface and 18.8 for height ratio; the figures ranged from 2.57 to 1.34 and from 26.1 to 13, respectively.

Policeman Group.—This group included forty members of the Changsha civil police force and represents the average young adult male of Changsha engaged in a moderately active outdoor occupation. The same correction for uniform and shoes was made as for the soldiers. The averages here were slightly higher, being 2.09 for surface and 19.7 for height; the extremes ran from 2.82 to 1.45 for the former and from 27.4 to 13 for the latter.

Workman Group.—This group included forty-nine artisans from different trades, including carpenters, masons, painters, weavers, printers, shoe-makers and barbers. This is more of a social classification than a similar type of labor. Hours of work are long, from twelve to sixteen hours a day. The ages run from 17 to 40. Three pounds (1.4 kg.) were deducted for weight of clothes and 8 cm. for height of shoes. An average of 2.03 for surface and 19.5 for height was obtained, the upper and lower limits being 2.69 and 1.37 for surface ratio and 26.1 and 12.8 for height.

12. DuBois, D., and Dubois, E. F.: Clinical Calorimetry. Tenth paper. A formula to Estimate the Approximate Surface Area if Height and Weight be Known, Arch. Int. Med. **17**:863 (June) 1916.

Shop Clerks.—Forty men were obtained from one of the silk stores in the city. They represent a fairly well-to-do class in a sedentary occupation. Records were taken in the shop at the end of the day's work. Three pounds (1.4 kg.) were deducted for clothes and 1 cm. for shoes. These men are the smallest in size and have the lowest ratios of any group of men except the soldiers, being 1.90 liters per square meter of body surface and 17.6 c.c. per centimeter of height. The extremes were 2.39 and 1.13 for surface and 21.9 and 10.2 for height.

House Coolie Group.—Altogether, forty-nine subjects of this group were studied. They were the indoor coolies [13] of the Hunan-Yale Hospital and Changsha Y. M. C. A. Their hours of work are long, but the work is not arduous, being mostly that of the janitor, housemaid, orderly, doorkeeper, watchman, or messenger type, etc. Four pounds (2 kg.) were deducted from the weight and 1 cm. from the height. Figures for this group were 2.12 surface ratio and 20.5 for height, the maximum being 2.68 and 25.5, the minimum 1.79 and 17.1, respectively.

Ricksha Coolie Group.—These men put in long hours pulling, generally on the run, the two wheeled passenger jinrickshas. This is the common method of travel in the large cities, and one would expect the coolies to develop extraordinary powers of endurance and wind, as the work is quite exhausting. In Changsha the rough streets do not permit great speed, so the work is a little harder than the ordinary coolie labor. Forty men were studied. The ages ranged from 20 to 50. All were barefoot; only 2 pounds (1 kg.) were subtracted for clothes. The average for this group was 2.01 for surface ratio and 19.3 for height, the upper and lower limits being 2.5 and 1.5 for surface, 23.5 and 14 for height. It is likely that in Shanghai, Hankow, Peking, or other better paved cities, the figures for this group would differ.

Carrying Coolie Group.—Forty of this type of laborer were obtained in two of the coolie guilds in the city. These men carry heavy burdens suspended from a pole which is carried on the shoulder. A large part of the freight in China is handled in this manner. It is heavy work and the men are noted for their endurance. They represent a group of strong and muscularly developed workers. They were barefoot; 2 pounds were deducted for clothes. The results for this group were 2.01 for surface and 19.7 for height ratios, the figures ranging from 2.54 to 1.65 and from 26.5 to 15.7, respectively.

Glassblowers' Group.—In this group also forty were studied. They were found in two glass factories in the city. This is a hard working group; blowing glass puts a great strain on the expiratory muscles, and one would expect an increase in lung capacity. They were barefoot;

13. "Coolie" is the Eastern term for the common laborer.

2 pounds were deducted from the weight. The surface ratio for this group was 2.13; for height, 20.3. The extremes were 2.52 and 1.5 for the former, 25.2 and 14 for the latter.

Students' Group.—There were thirty-six in this group, including medical students, hospital interns and a few male nurses. The ages ranged from 19 to 31. These represent a rather picked group of normal active young adults, although they are more athletic than the ordinary Chinese. A correction of 4 pounds was made for clothes and 1 cm. for shoes. The averages for this group were 2.18 surface and 21 height ratio; the figures ranged from 2.56 to 1.74 for the former and 25.6 to 16.4 for the latter.

Female Students.—In this group were seventy-five girls, from 16 to 22 years of age, from the Fu Siang Girls' School and from the Hunan-Yale School of Nursing. All had had physical examinations before these records were taken. The group represents the average well-developed Chinese young woman. The height and weight figures show what small bodies most of the girls have. No correction was made for clothing. The averages here were 1.54 for surface and 14.3 for height ratio, with the extremes of 2.08 and 0.99 for the former, 19.4 and 9.2 for the latter.

Foreigners' Group.—The records of twenty-five occidentals were obtained for comparison with the Chinese. In this group were included physicians of the hospital staff, teachers in the College of Yale in China, local business men and some sailors from the U. S. S. *Quiros*. The ages ranged from 19 to 48. No deductions were made for clothing, so the results are slightly lower than if measurements were taken stripped. The averages for the group were 2.39 liters per square meter of body surface and 25.1 c.c. per cubic millimeter of height. The extremes here were 2.87 and 1.64 for surface, with 31.8 and 18.9 for height ratios.

COMMENT

A study of the vital capacity of 425 men and seventy-five women in different groups of Chinese (Table 1) shows a general average of 2.02 liters per square meter of body surface for the men and 1.53 for the women. For convenience, the flat figures of 2 and 1.5 have been adopted as the normal standard for surface ratio for men and women, respectively. An analysis of the individual cases according to occupational groups (Table 2), shows only 42 per cent. of the men and 51 per cent. of the women within plus or minus 10 per cent. of the standard; about 20 per cent. of both men and women are below 90 per cent. Compared with the American standard of 2.5 for men and 2 for women, we find that 80 per cent. of the men and 85 per cent. of the women fall below 90 per cent. of the normal.

TABLE 1.—*A Comparison of the Vital Capacity Measurements of Eleven Occupational Groups of a Total of Five Hundred Chinese*

Group	No.	Average Vital Capacity, C.c.	Average Height, Cm.	Average Weight, Kg.	Average Body Surface Ratio, Liters per Sq. M.	Average Body Surface, Liters per Sq. M.	Height Ratio, C.c. per Cm.
Soldiers	97	3,070	164.0	58.0	1.63	1.89	18.8
Policemen	40	3,270	166.0	53.4	1.55	2.09	19.7
Workmen	49	3,160	162.0	54.0	1.55	2.03	19.5
Shop clerks	40	2,840	161.0	49.1	1.49	1.90	17.6
House coolies	43	3,320	161.0	54.8	1.56	2.12	20.5
Ricksha coolies	40	3,050	160.0	53.8	1.54	2.01	19.3
Carrying coolies	40	3,240	165.0	56.8	1.61	2.01	19.7
Glassblowers	40	3,280	162.0	52.3	1.54	2.13	20.3
Students	36	3,520	167.0	55.2	1.60	2.18	21.0
Average of	425	3,180	163.0	54.7	1.58	2.02	19.5
Women	75	2,240	157.0	47.7	1.45	1.54	14.3
Foreigners	25	4,300	174.0	69.6	1.83	2.39	25.1

TABLE 2.—*Percentage Relation of Surface Ratios to Standards*

Group	No.	Average Surface Ratio, Liters per Sq. M.	% Local Standard, 2 Liters per Sq. M.	Above 110 per Cent. No.	Above 110 per Cent. Per Cent.	Below 90 per Cent. No.	Below 90 per Cent. Per Cent.	Below 80 per Cent. No.	Below 80 per Cent. Per Cent.	% West's Standard, 2.5 Liters per Sq. M.	Below 90 per Cent. No.	Below 90 per Cent. Per Cent.
Soldiers	97	1.89	95	7	7	31	32	15	15	75	94	97
Policemen	40	2.09	105	16	40	8	20	2	5	84	28	70
Workmen	49	2.03	102	9	18	8	16	1	2	81	44	90
Clerks	40	1.90	95	8	20	12	30	6	15	76	33	82
House coolies	43	2.12	106	15	35	1	2	..	..	85	31	72
Ricksha coolies	40	2.01	100	12	30	9	22	4	10	80	30	75
Carrying coolies	40	2.01	100	11	28	10	25	..	..	80	30	75
Glassblowers	40	2.13	107	16	40	2	5	2	5	85	28	70
Students	36	2.18	109	17	47	2	6	..	..	87	22	61
Average of	425	2.02	101	111	26	83	19	30	7	81	340	80
Foreigners	25	2.39	119	20	80	1	4	..	..	96	7	28
			Local Standard, 1.5 Liters per Sq. M.							West's Standard, 2 Liters per Sq. M.		
Women	75	1.54	102	22	29	15	20	3	4	72	64	86

TABLE 3.—*Percentage Relation of Height Ratios to Standards*

Group	No.	Average Height Ratio, C.c. per Cm.	Local Standard, 19 per Cm.	Above 110 per Cent. No.	Above 110 per Cent. Per Cent.	Below 90 per Cent. No.	Below 90 per Cent. Per Cent.	Below 80 per Cent. No.	Below 80 per Cent. Per Cent.	West's Standard, 20 per Cm.	Below 90 per Cent. No.	Below 90 per Cent. Per Cent.
Soldiers	97	18.8	99	17	18	25	26	11	11	75	92	95
Policemen	40	19.7	104	20	50	10	25	2	5	79	35	87
Workmen	49	19.5	103	15	30	8	16	1	2	78	47	96
Clerks	40	17.6	90	7	17	17	42	9	22	70	40	100
House coolies	43	20.5	108	17	39	..	..	..	..	80	35	81
Ricksha coolies	40	19.3	101	12	30	9	22	3	7	77	36	90
Carrying coolies	40	19.7	104	12	30	7	17	..	..	78	34	85
Glassblowers	40	20.3	107	15	38	4	10	2	5	81	31	78
Students	36	21.0	111	19	53	3	8	..	..	84	24	67
Average of	425	19.5	102	134	31	83	19	28	7	78	374	88
Foreigners	25	25.1	132	21	84	..	..	..	..	100	6	24
			Local Standard, 14 C.c. per Cm.							West's Standard, 20 C.c. per Cm.		
Women	75	14.3	102	22	29	17	23	5	7	70	70	93

Height ratios show an average of 19.5 c.c. per centimeter of body height for men and 14.3 for women. The flat figures of 19 and 14 were taken as the normal standard. A study of the individual and group variations (Table 3) shows a general similarity to the body surface ratios; only 50 per cent. of the men and 48 per cent. of the women are within 10 per cent. of standard, with approximately the same proportion as above falling below 90 per cent. The height ratios seem to show a wider range, yet, on the whole, follow the surface ratios closely. Compare these results with the Western standards of 25 c.c. per centimeter of height for men and 20 for women, and we find that only fifty-one men and five women are within 90 per cent. of those figures, that is, 88 per cent. of the men and 93 per cent. of the women are below 90 per cent.

A comparison of the averages of the occupational groups shows some differences which seem to be greater than the normal error. The soldiers have the lowest vital capacity with an average surface ratio of 0.13 below the general average, while the students are the highest with 0.16 above. The reason for the low figures for this group of soldiers is not apparent, although one is tempted to question their physical fitness. The shop clerks, with little physical work, have a low lung capacity, almost as low as that of the soldiers. The coolies of different types have about the same ratios. It is surprising that the ricksha coolies have not a higher vital capacity, their capacity being lower than that of the house coolies whose work is chiefly indoors. The glass blowers, as expected, have the highest capacity of all the laborers, although theirs is lower than that of the students. The students, on the whole, had been fairly active in sports, basket ball and soccer football, and it would seem as though athletics were the important factor in this case. This seems to confirm the doubt raised by Hewlett and Jackson that standards based on a picked group, such as college students, are too high for the general public.

The average for women is much lower than for men. This is in keeping with the difference noted by West, and the proportion is approximately the same. It is interesting to note that the figures for women are lower than those obtained for schoolchildren from 6 to 16 years of age in New York City.

The group of foreigners gives an average surface ratio of vital capacity of 2.39. This is low as compared with West's standard; seven of the twenty-five being below 90 per cent. The height ratio of 25.1 for the group equals the standard for Americans. The group, as a whole, which includes several overweight and quite sedentary persons, is more than 15 per cent. greater in both surface and height ratios than the Chinese. As the measurements were taken under the same conditions, a racial factor is strongly suggested. No vital capacity studies on

other Eastern races have been found for comparison. It has been noted, however, that the figures for negro children in the United States are less than for the white children of the same ages.[3]

In this study, the height ratios give nearly as uniform results, although there is more variation in the extremes. This method is simpler, and for rapid calculation in clinical work is probably preferable.

Figures obtained for Chinese in Central China will not necessarily hold true for the whole country, since there is a great difference in the stature and physical development of the different races of the Chinese.

SUMMARY

1. The vital capacity in 500 Chinese in eleven occupational groups, including a number of young women, has been studied and analyzed.

2. A normal standard of 2 liters per square meter of body surface for men and 1.5 for women was obtained.

TABLE 4.—*Summary of Normal Standards*

	Vital Capacity Body Surface, Liters per Square Meter	Vital Capacity Height, C.c. per Centimeter
Americans:		
Men [4]	2.5	25.0
Women [4]	2.0	20.0
Children [5]	1.93	15.5
"Athletes" [4]	2.8	29.0
Chinese:		
Men	2.0	19.0
Women	1.5	14.0

3. A normal standard of 19 c.c. per centimeter of body height for men and 14 for women may also be used with little less accuracy.

4. Various factors were noted which affect the vital capacity: (*a*) Men show a vital capacity 31 per cent. greater than women. (*b*) Occupations seem to influence the vital capacity to some extent, although not in proportion to the degree of physical activity. (*c*) Athletics tend to increase the vital capacity.

CONCLUSIONS

The Chinese show much lower vital capacity ratios than Westerners.

Standards based on a picked group of persons cannot be applied uniformly to all groups.

BLOOD SUGAR REACTION FOLLOWING INTRAVENOUS INJECTION OF GLUCOSE *

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MINNEAPOLIS

The literature dealing with the alimentary glucose tolerance test [1] has been recently reviewed by Macleod,[2] Folin and Berglund,[3] John,[4] MacLean and de Wesselow.[5] In addition to its use as a diagnostic aid in diabetes, according to Sherrill,[6] John [4] and others, it has assumed importance in a wide variety of diseases.[7] Janney and Isaacson [8] have improved on the technic as first applied. By doing both blood and urine sugar analyses, the factor of renal permeability has been overcome so that it is rather a reading of glycemia than of glycosuria. In addition, the amount of glucose to be given varies with the weight of the person.

Intestinal absorption, as a variable factor, has long been recognized. Janney and Isaacson [8] discuss this at length and point to the work of Janney [9] and of Fisher and Wishart [10] to prove that it is unimportant. Their proof is not convincing. They state that 66 per cent. of the ingested glucose will be absorbed within an hour. The constancy of the blood sugar curve obtained in normal persons is also used as an indication that the absorption is fairly constant. Woodyatt [11] and Wilder and Sansum [12] have called attention to the time element in the metabolism of carbohydrates. If the absorption time is inconstant, the test as ordinarily done, by giving the glucose by mouth, leaves this time

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1. The term "tolerance test" is used here only to correlate this work with that previously done on this subject. It is hardly justifiable from our meager knowledge of carbohydrate metabolism to term this a test of glucose tolerance. We feel that it should rather be called the "blood sugar reaction to glucose" as that expresses our actual knowledge of the processes taking place.

2. Macleod, J. J. R.: Physiol. Rev. **1**:208, 1921.

3. Folin and Berglund: J. Biol. Chem. **51**:413, 1922.

4. John, H. J.: J. Metabolic Res. **1**:498, 1922.

5. MacLean and de Wesselow: Quart. J. Med. **14**:103, 1921.

6. Sherrill, J. W.: The Diagnosis of Latent or Incipient Diabetes, J. A. M. A. **77**:1779 (Dec. 3) 1921.

7. Olmsted, W. H., and Gay, L. P.: Study of Blood Sugar Curves Following a Standardized Glucose Meal, Arch. Int. Med. **29**:384 (March) 1922.

8. Janney, N. W., and Isaacson, V. I.: A Blood Sugar Tolerance Test, J. A. M. A. **70**:1131, 1918.

9. Janney, N. W.: J. Biol. Chem. **22**:203, 1915.

10. Fisher and Wishart: J. Biol. Chem. **13**:49, 1912.

11. Woodyatt, R. T.: Harvey Lectures, **11**:326, 1915.

12. Wilder, R. M., and Sansum, W. D.: A Glucose Tolerance in Health and Disease, Arch. Int. Med. **19**:311, 1917.

factor out entirely.[13, 14] The best evidence submitted to show that gastro-intestinal absorption is exceedingly variable is the recent work of Fitz and his co-workers.[15] One hour after giving 100 gm. of glucose, they passed a duodenal tube into the stomach and aspirated as much of the stomach contents as possible, titrating it for glucose. They recovered from 22 per cent. to 68 per cent. of the amount given, the results in all cases being very different and the variability appearing to be due to individual idiosyncrasy rather than to any rule. They also gave varying amounts in solutions of different percentages with an even greater variation in the amount recovered at the end of an hour.

Goldschmidt's[16] review of the subject of intestinal absorption is sufficient to show how many factors enter into it and how variable it must be in different persons. Bergmarck[17] and Mertz and Rominger[18] have demonstrated the difference it might make in tests on children. The latter gave glucose by mouth and plotted a curve of the blood sugar reaction. They repeated the test on the same persons under similar conditions except that tannic acid was added to the glucose. The curves obtained were radically different, the first being much higher than the second. The tannic acid, apparently by its astringent action, had caused a decreased absorption with a slower flooding of the circulation and thus a lower blood sugar curve.

If the factor of gastro-intestinal absorption is of such importance, it is obvious that many of the tests done are worthless. To overcome this factor and for experimental purposes, glucose has been given subcutaneously, intramuscularly and intravenously. The first two methods are, of course, affected by the uncertain factor of absorption. The old and recent literature on intravenous glucose injections has been amply reviewed by Wilder and Sansum,[12] Kleiner,[19] Nonnenbruch and Szyszka[20] and Bang.[21] Blumenthal,[13] in 1904, attempted to determine glucose tolerance by the intravenous method, but he made no blood sugar estimations, depending on the production of glycosuria and leaving out of consideration the permeability of the kidneys. In 1913, Tannhauser and Pfitzer[14] made the first clinical attempt to determine the hyperglycemia caused in man by the injection of small amounts of glucose solution into a vein. They plotted curves for normal persons, persons with chronic nephritis, liver diseases and diabetes. In 1916,

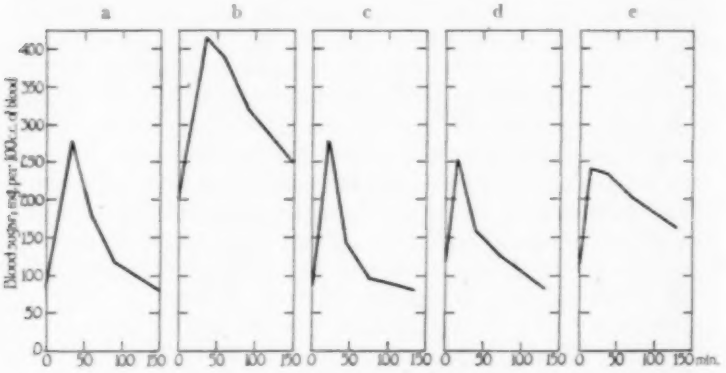
13. Blumenthal, F.: Beitr. z. chem. Phys. u. Path. **6**:329, 1905.
14. Tannhauser and Pfitzer: München. med .Wchnschr. **9**:2155, 1913.
15. Beeler, Bryan, Cathcart and Fitz: J. Metabolic Res. **1**:549, 1922.
16. Goldschmidt, S.: Physiol. Rev. **1**:421, 1921.
17. Bergmarck: Jahrb. f. Kinder. **80**:373, 1914.
18. Mertz and Rominger: Arch. f. Kinder. **69**:81, 1921.
19. Kleiner, I.: J. Exper. M. **23**:507, 1916.
20. Nonnenbruch and Szyszka: Arch. f. Exper. Path. u. Pharm. **86**:281, 1920.
21. Bang, I. C.: Der Blutzucker, Wiesbaden, 1913.

Woodyatt [11] and Wilder and Sansum [12] introduced timed intravenous injections by means of an electric pump. They gave varying amounts of glucose solutions of different concentrations within definite time limits and determined the amount which could be given per hour without glycosuria. They did not, however, attempt to show the amount of hyperglycemia which resulted. Allen and Wishart [22] gave glucose intravenously to partially and completely depancreatized dogs and concluded that the method is a good one for making tolerance tests if the blood sugar estimations are properly controlled by urine examinations. If too much sugar appears in the urine, it may cause a distinct depression in the blood sugar. Titus and Givens [23] have given glucose intravenously to women with toxemia of pregnancy in 20 to 25 per cent. solution and have plotted blood sugar curves. Opitz,[24] Beumer,[25] and Nonnenbruch and Szyszka [29] have recently made sugar tolerance tests in this way. The latter also have followed the red blood corpuscle count, the serum albumin, the serum sodium chlorid, and the relative volume percentage of the serum and corpuscles. They found definite evidences of a hydremia following the glucose injections. All their cases showed also a rise in the blood sugar shortly after the injection, followed by a drop to normal in most cases.

In the hope of devising a glucose tolerance test which would be free from the variable and uncertain factor of gastro-intestinal absorption, we have given 20 per cent. solutions of glucose intravenously to a number of nondiabetic and diabetic persons taken from the medical wards of the Minneapolis General Hospital. All the tests were performed on a basal level, at least sixteen hours after the last food had been taken. The glucose given was a highly purified dextrose, dissolved in distilled water, filtered and sterilized in an autoclave for thirty minutes under 10 to 15 pounds (4.5 to 6.8 kg.) of pressure. The solution was given by means of the pressure flask of Hoffman and Habein,[26] carefully graduated and timed in such a manner that the flow was fairly constant, the amount and the time in which it was given, exact. Other methods of giving timed intravenous solutions have been described by Freidell,[27] Thalhimer,[28] and Korbsch,[29] but we have

22. Allen and Wishart: J. Biol. Chem. **42**:415, 1920.
23. Titus, P., and Givens, M. H.: Intravenous Injections of Glucose in Toxemia of Pregnancy, J. A. M. A. **78**:92, 1922.
24. Opitz, H.: Klin. Wchnschr. **1**:117, 1922.
25. Beumer, H.: Zschr. f. Kinder. **29**:352, 1921.
26. Hoffman, M. H., and Habein, H. C.: Transfusion of Citrated Blood, J. A. M. A. **76**:358 (Feb. 5) 1921.
27. Freidell, H. F.: Apparatus for Continuous Intravenous Administration of Fluids by Which the Rate of Flow May Be Easily Determined and Controlled, J. A. M. A. **76**:724 (March 12) 1921.
28. Thalhimer, W.: A Simple Apparatus for Accurate Intravenous Administration of Glucose Solutions, J. A. M. A. **78**:190 (Jan. 21) 1922.
29. Korbsch, R.: München. med. Wchnschr. **67**:936, 1920.

found the pressure flask eminently satisfactory. It is obvious that the electric pump would be the best method, but this is not generally obtainable. The first sample of blood was collected through the same needle through which the dextrose solution was injected. A second sample was collected five minutes after the injection was completed; a third, thirty minutes after; a fourth, sixty minutes after; a fifth, one hundred and twenty minutes after. Urine was collected for this whole period and for twenty-four hours after in most cases and examined for sugar by the well-known Benedict quantitative method. The samples of blood were all obtained by venipuncture, collected in sodium oxalate, and analyzed shortly after for sugar by the Benedict modification of the Lewis-Benedict method. On many of the cases, separate determinations of whole blood and plasma were made. We



Typical curves from each group of cases illustrating blood sugar reaction of nondiabetic and diabetic to intravenous glucose administration. Blood sugar expressed in milligrams per 100 cubic centimeters of blood on ordinates. Time elapsing from beginning of injection to the collecting of the blood expressed in minutes on abscissas. *A* indicates nondiabetic patients given 1 gm. of glucose per kilogram of body weight in thirty minutes (Case 4, Table 1); *B*, diabetic patient given 1 gm. of glucose per kilogram of body weight in thirty minutes (Case 12, Table 1); *C*, nondiabetic patient given 0.5 gm. of glucose per kilogram of body weight in fifteen minutes (Case 19, Table 2); *D*, nondiabetic patient given 0.33 gm. of glucose per kilogram of body weight in ten minutes (Case 29, Table 3); *E*, diabetic patient given 0.33 gm. of glucose per kilogram of body weight in ten minutes (Case 37, Table 3).

found that we could not centrifuge the blood rapidly enough to prevent the interchange which takes place rapidly in vitro between corpuscles and plasma. The results were interesting but were no doubt inaccurate and therefore are not published. In most of the cases red blood corpuscle counts were made at the same time that the blood was collected for sugar analysis. This was done to determine whether or not

hydremia occurred, in accordance with the findings of Fisher and Wishart,[19] Sherrill and John,[30] Nonnenbruch and Szyszka [20] and others.

The cases are divided into three groups: The first (Table 1), including ten nondiabetic and five diabetic patients, were given 1 gm. of glucose per kilogram of body weight, the duration of the injection being 30 minutes. The second group (Table 2), including thirteen nondiabetic patients, were given 0.5 gm. of glucose per kilogram of body weight in fifteen minutes. The third group (Table 3), including seven nondiabetic and three diabetic patients, were given 0.33 gm. of glucose per kilogram of body weight in ten minutes. A 20 per cent. solution was used throughout. The tables given below show the results obtained. Blood sugar is tabulated in milligrams per one hundred cubic centimeters of blood. Red blood corpuscle counts are tabulated on a basis of percentages, the count before injection being considered as 100 per cent. The quantity of sugar appearing in the urine, the total amount of glucose given, the age of the patient, and the diagnosis of each case are also shown. Five curves have been plotted to illustrate each type of case. All are shown in the chart. The first (*a*) is Case 4, a nondiabetic patient, given 1 gm. of glucose per kilogram of body weight in thirty minutes. The second (*b*) is Case 12, a diabetic given 1 gm. of glucose per kilogram of body weight in thirty minutes. The third (*c*) is Case 19, a nondiabetic patient given 0.5 gm. glucose per kilogram of body weight in fifteen minutes. The last two were given 0.33 gm. of glucose per kilogram of body weight in ten minutes. The fourth (*d*) represents Case 29, a nondiabetic patient. The fifth (*e*) represents Case 37, a diabetic patient.

It can readily be seen from the red blood corpuscle counts that in most cases, at least, a hydremia occurs which has a tendency to decrease in direct ratio to the decrease in blood sugar. The characteristic finding in regard to the blood sugar is the marked rise occurring just after the injection, followed by a definite fall to normal usually within one hour, and almost invariably a fall to subnormal at the end of two hours. It appears that the latter is just as important and constant as any of the other characteristics of the normal curve. It is difficult to make a statement from these cases as to the normal curve, because they are not true normals. However, it can be concluded from the examination of all the curves that the normal should show a high rise in the blood sugar just after the injection, a drop to about 50 per cent. above the fasting level at the end of thirty minutes, a normal reading at sixty minutes, and a subnormal reading at one-hundred twenty minutes. The diabetic patients show the results which can be expected. The rise just after the injection is much

30. Sherrill and John: J. Metabolic Res. **1**:109, 1922.

TABLE 1.—*Results on Ten Nondiabetic and Five Diabetic Persons Given 1 Gm. Glucose per Kilogram of Body Weight in 20 Per Cent. Solution Intravenously in Fifteen Minutes**

Case Number	Specimen Numbers †										Urine Sugar, Gm.	Body Weight, Kg.	Glucose, Total Amount, Gm.	Age of Patient	Remarks
	1		2		3		4		5						
	Blood Sugar, Mg.	Red Blood Corpuscles, %	Blood Sugar, Mg.	Red Blood Corpuscles, %	Blood Sugar, Mg.	Red Blood Corpuscles, %	Blood Sugar, Mg.	Red Blood Corpuscles, %	Blood Sugar, Mg.	Red Blood Corpuscles, %					
1	125	100	436	78	333	92	279	82	104	92	8.64	75	75	38	Acute arthritis; convalescent
2	145	100	325	83	121	91	111	96	79	83	4.5	62	62	40	Acute arthritis; convalescent
3	80	100	307	72	206	82	121	91	78	80	1.1	70	70	39	Chronic bronchitis
4	85	100	279	98	185	70	121	...	80	105	Trace	52	52	67	Chronic bronchitis; syphilis
5	118	100	434	99	300	95	157	94	65	...	3.25	75	75	65	Essential hypertension; cardiac hypertrophy
6	101	100	320	87	...	91	192	94	88	102	....	55	55	54	Cardiac valvular disease; No. 3 lost
7	86	100	226	93	105	92	143	98	95	113	4.04	52	52	41	Pleurisy, tuberculous
8	124	100	...	...	272	75	212	55	135	78	1.05	61	61	48	Syphilitic cirrhosis of liver; slight temperature reaction
9	97	100	151	74	115	95	87	...	82	110	0.0	45	45	60	Carcinoma of stomach, with metastasis to bowels; cachexia
10	101	100	356	72	255	45	174	71	56	91	....	71	71	40	Obstructive jaundice; syphilis; cholelithiasis
11	164	100	380	95	318	110	234	86	124	102	2.4	67	67	43	Very mild diabetes
12	204	100	416	84	390	105	323	120	251	104	4.1	47	47	24	Moderately severe diabetes
13	212	100	340	82	215	87	311	87	307	90	10.7	50	50	61	Severe diabetes
14	333	100	406	85	406	90	358	96	314	97	15.0	50	50	45	Severe diabetes
15	461	100	727	76	533	87	492	92	492	91	10.0	40	40	50	Very severe diabetes

* Blood sugar recorded in milligrams per hundred cubic centimeters of blood. Red blood corpuscle counts made at the same intervals as the blood sugar are charted on a percentage basis, the first count being considered 100 per cent. Urine sugar for the whole period is shown, as well as the total quantity of glucose given. The diagnosis and age of each case are tabulated.

† Blood sugar determinations: No. 1, before injection; No. 2, five minutes after; No. 3, thirty minutes after; No. 4, sixty minutes after; No. 5, 120 minutes after.

TABLE 2.—*Results on Thirteen Nondiabetic Persons given 0.5 Gm. Glucose per Kilogram of Body Weight in 20 Per cent. Solution Intravenously in Fifteen Minutes**

Case Number	Specimen Numbers †										Urine Sugar, Gm.	Body Weight, Kg.	Glucose, Total Amount, Gm.	Age of Patient	Remarks
	1		2		3		4		5						
	Blood Sugar, Mg.	Red Blood Corpuscles, %	Blood Sugar, Mg.	Red Blood Corpuscles, %	Blood Sugar, Mg.	Red Blood Corpuscles, %	Blood Sugar, Mg.	Red Blood Corpuscles, %	Blood Sugar, Mg.	Red Blood Corpuscles, %					
16	98	100	205	65	228	79	124	83	54	93	1	60	30	73	Carcinoma of stomach
17	155	100	182	77	116	83	91	89	85	95	0	52	26	46	Syphilitic aortitis
18	76	100	240	74	124	79	...	...	76	85	....	48	24	50	Cardiac hypertrophy; chronic asthma; No. 4 lost
19	87	100	279	92	145	83	98	81	81	79	2.2	55	27.5	23	Exophthalmic goiter
20	122	100	328	91	207	80	146	86	111	92	....	45	22.5	76	Hypertension; cardiac hypertrophy; arteriosclerotic nephritis
21	101	100	278	77	125	84	...	...	77	88	1	60	30	79	Essential hypertension; No. 4 not taken; No. 5 at 90 minutes
22	145	100	242	79	206	84	183	86	161	95	....	80	40	60	Hypertension; cardiac hypertrophy
23	122	100	234	76	211	76	132	85	121	93	....	82	41	53	Cardiac hypertrophy; syphilis
24	107	100	214	84	143	96	...	...	86	98	....	80	40	73	Chronic arthritis; No. 4 not taken; No. 5 at 90 minutes
25	110	100	340	81	230	73	...	...	92	81	....	43	21.5	75	Chronic bronchitis; No. 4 not taken
26	104	100	306	81	241	81	178	81	...	...	0.5	35	17.5	55	Chronic tuberculosis; No. 5 not taken
27	76	100	338	96	171	85	107	97	65	101	....	80	40	72	Senility; fractured femur
28	107	100	285	84	138	90	86	95	80	96	0	68	34	43	Scleroderma; No. 5 taken at 90 minutes

* Blood sugar recorded in milligrams per hundred cubic centimeters of blood. Red blood corpuscle counts made at the same intervals as the blood sugar are charted on a percentage basis, the first count being considered 100 per cent. Urine sugar for the whole period is shown, as well as the total quantity of glucose given. The diagnosis and age of each case are tabulated.

† Blood sugar determinations: No. 1, before injection; No. 2, five minutes after; No. 3, thirty minutes after; No. 4, sixty minutes after; No. 5, 120 minutes after.

higher; there is only a small depression at the end of thirty minutes; at the end of sixty minutes the blood sugar is still far above the fasting level; at the end of 120 minutes it is still above the fasting level or just at it. The difference between the normal persons and the mild diabetic patient can be seen by a comparison of the curves shown. The curves as a whole resemble those obtained by the alimentary method, but the action is more rapid.

We do not feel that, in the consideration of this test, the excretion of sugar in the urine is an important finding, except in so far as a large excretion of sugar be accompanied by a rapid fall in the blood sugar. This does not occur when using the smallest dose, so that it need not be seriously considered. It is of interest to note that in many

TABLE 3.—*Results on Seven Nondiabetic and Three Diabetic Persons Given 0.33 Gm. Glucose Per Kilogram of Body Weight in 20 Per Cent. Solution in Ten Minutes* *

Case Number	Specimen Numbers †					Urine Sugar, Gm.	Body Weight, Kg.	Glucose, Total Amt., Gm.	Age of Patient	Remarks
	1	2	3	4	5					
29	119	254	161	131	82	0	57	19	51	Chronic cardiac valvular disease
30	98	220	166	...	94	..	66	22	58	Essential hypertension; No. 4 not taken
31	90	182	147	87	86	0	60	20	70	Essential hypertension
32	112	272	182	...	81	0.66	60	20	60	Chronic duodenal ulcer; No. 4 not taken
33	80	234	142	117	91	..	67	22.3	53	Chronic arthritis
34	82	237	174	99	72	0	69	23	68	Bronchial asthma
35	84	200	136	104	88	0	43	14.2	43	Carcinoma of stomach with metastasis to liver
36	163	365	294	233	166	0	81	27	55	Moderately severe diabetes
37	120	241	228	206	164	2	52	17.3	62	Mild diabetes
38	326	601	483	441	365	Trace	43	14.3	62	Severe diabetes

* Blood sugar recorded in milligrams per hundred cubic centimeters of blood. Urine sugar for the whole period is shown, as well as the total quantity of glucose given. The diagnosis and age of each case are given.

† Blood sugar determinations: No. 1, before injection; No. 2, five minutes after; No. 3, thirty minutes after; No. 4, sixty minutes after; No. 5, 120 minutes after.

cases in which the blood sugar rose to a figure far above 200 mg. per one hundred c.c., no sugar was excreted. This may be due to the fact that the elevation of the blood sugar was too transitory to produce a glycosuria.

The amount of glucose given and the duration of the injection are of course important considerations, as can easily be seen from our results. The three different methods used were purely experimental. We feel that the last method, giving 0.33 gm. of glucose per kilogram of body weight in ten minutes is the best, as it is easiest to give, does not cause such marked elevation in the blood sugar, and seldom produces marked glycosuria. It is possible that even smaller doses might be still more desirable. It should be noted that none of the cases used

can be considered normal in the strictest sense of the word, as they were taken from the wards, and we have classified them simply as diabetic and nondiabetic. For this reason we do not feel justified in presenting any of these results as definitely indicative of the normal reaction.

As we have plotted no definite normal curve, we hesitate to call attention to the curves presented by the various types of cases. In addition, our series of each type is too small to permit of drawing any conclusions. Our object in this work has been rather to determine whether the method is feasible and, in a general way, what the response would be on the part of the patient. The curves of a large series of normal patients should be determined by this method, following which the curves typical of different diseases might be plotted.

Many objections can no doubt be raised against this method of making sugar tolerance tests. Janney and Isaacson [9] object to the venipunctures, but this is hardly valid, as these are necessary in doing any but the micro tests for blood sugar. The objection that this method is not physiologic in that it leaves the portal system out of consideration, is more difficult to answer. It has been shown by Tannhauser and Pfitzer [14] that the liver plays an important part in the disposition of glucose even when injected intravenously, as their most abnormal curves were obtained in diseases of the liver. Folin and Berglund [3] point out that the tissues of the body, as a whole, play fully as important a part in carbohydrate metabolism as the liver. The chief objection that must be answered is that the injection of glucose solutions into a vein is not a harmless procedure and should therefore not be indulged in at random. The use of a purified dextrose, well dissolved and sterilized, should obviate any danger. Budingen [31] has given 4,500 injections for therapeutic purposes without one untoward result. Kausch,[32] Korbsch,[33] Lyon,[34] and Haden,[35] and a host of others report similar results. In our own series, we have had only one case in which there was a slight chill followed by a temperature of 99.2 F. In addition to this, two patients who were having an intermittent temperature showed rises of temperature to 100 and 100.4 F., respectively, but it is doubtful that these could be assigned to the glucose injections. The difficulty in giving the intravenous solution can also be considered an objection, but with a little practice it can be done with facility.

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31. Budingen, T.: Deutsch. Arch. f. klin. Med. **128**:151, 1918.
32. Kausch, W.: Deutsch. med. Wchnschr. **37**:8, 1911.
33. Korbsch, R.: Deutsch. med. Wchnschr. **47**:332, 1921.
34. Lyon, G.: Arch. Pediat. **36**:161, 1919.
35. Haden, R. L.: Therapeutic Application of the Alteration of Brain Volume by the Intravenous Injection of Glucose, J. A. M. A. **73**:983 (Sept. 27) 1919.

The subject has fertile possibilities. We have not attempted to present any definite standards, but merely offer this method as a suggestion for future use. We feel that we have demonstrated its simplicity, feasibility, and its superiority to the alimentary test in determining a variation in carbohydrate metabolism. Intravenous tolerance tests in the past have been so variable in their methods and technic that adequate comparison is impossible. More work should be done by this method to establish standards, and this can only be done if a uniform technic is used. The purpose of this paper has been to suggest such a technic and to demonstrate its applicability to the test.

SUMMARY AND CONCLUSIONS

The alimentary glucose tolerance test is objectionable chiefly because of the great variability in gastro-intestinal absorption time rendering it inaccurate and misleading.

The previous work on intravenous glucose tolerance tests is discussed. The methods and technic used by the authors in making glucose tolerance tests by the intravenous method on thirty-eight cases is presented and the results shown in tables and curves.

The differences between the normal reaction of the blood sugar to the intravenous injection of glucose and the diabetic reaction are shown. Glucose tolerance tests can be made far more accurately by giving glucose solutions intravenously and making blood sugar estimations at intervals afterward, than by the alimentary route.

The intravenous injection of glucose is a simple and harmless procedure. Further work should be done by this method to establish normal standards.

EXPERIMENTS WITH HODGKIN'S DISEASE

AN ATTEMPT TO PRODUCE IT IN ANTHROPOIDS AND OTHER MONKEYS *

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AND
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These experiments were made in an attempt to produce Hodgkin's disease in chimpanzees and rhesus monkeys. The apes were chosen because numerous attempts were made to produce this disease in lower animals. Feeding experiments and injections of gland extracts have been made on guinea-pigs, rabbits, ring tail and rhesus monkeys.[1] Certain hyperplasias have been produced, but it has been shown that the injection into animals of normal gland extracts causes a lymphatic hyperplasia.

For a working basis the following premises were adopted: 1. Hodgkin's disease is a distinct clinicopathologic entity. 2. It belongs to the group of infectious granulomas and is of bacterial or protozoan origin.

The results obtained were all negative, but it is believed that they should be recorded because the biologic similarity between chimpanzees and man make the findings of more significance in regard to the transmissibility of the disease by implantation of tissue.

ANIMALS

Before procuring the chimpanzees, it was necessary to learn something of the habits and living conditions of these animals, and many months were spent in veterinary consultations and going over plans for proper housing and caging. After securing the animals, the next step was to determine, as far as possible, that they were free from disease. Such conditions as eczema, pyorrhea alveolaris and round worms, were very troublesome. Wassermann tests were made and also complement-fixation tests for tuberculosis. The latter were felt to be important, owing to the susceptibility of apes to this disease. The two chimpanzees gave positive reactions, but they showed no evidence of tuberculosis while under our observation from Oct. 28, 1916, until May, 1920.

* This work was carried on under a grant from the Harriman research fund.

* From the laboratories of the department of surgery, Columbia University.

1. Reed: Bull. Johns Hopkins Hosp. No. 10, 1902, p. 135. Longcope: Bulletin Ayer Clinical Lab. No. 4, 1907. Bunting, C. H., and Yates, J. G.: An Etiologic Study of Hodgkin's Disease, J. A. M. A. **61**:1803 (Nov. 15) 1913; An Etiologic Study of Hodgkin's Disease, **62**:516 (Feb. 14) 1914. Schaeffer, E.: Berl. klin. Wchnschr. **51**:1215, 1914.

Apparently, tuberculosis runs its almost uniformly fatal course in these animals within eighteen months under the zoologic and circus conditions of New York City.

Fig. 1.—Low power reproduction of drawing of gland used in Experiment 1.

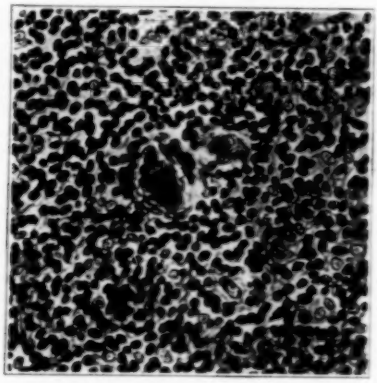

Fig. 2.—High power reproduction of drawing of gland used in Experiment 2.

Both chimpanzees were immature females. They were in the process of shedding their baby teeth and were judged by an expert from the Bronx Zoological Park to be about 4 years of age.

EXPERIMENTAL WORK

Experiment 1.—A group of three nodes was removed from a man, 23 years of age, who first noticed an enlargement in the neck eight months previously. Later lymphomas developed in the axillae. These showed the typical histologic picture of Hodgkin's disease (Fig. 1).

A slice of a node 1.5 by 0.3 cm. was transplanted into the retroperitoneal region and one 0.7 by 0.5 into the spleen of a rhesus. The animal was observed for five months, and no external evidence of Hodgkin's disease was noted.

The rhesus was then used for a poliomyelitis experiment and died. Necropsy was performed and microscopic examinations were made, but no evidence of Hodgkin's disease was found.

Fig. 3.—Low power reproduction of drawing of gland used in Experiment 3.

Experiment 2.—Glands were removed at the Roosevelt Hospital from the groins of a man, 30 years of age, who had been suffering from weakness, night sweats and lymphomas in the axillae, neck and groins.

Histologically the glands were those of Hodgkin's diseases (Fig. 2).

Bacteriologic examinations were made of the glands, but no organisms were isolated.

Two pieces of nodes, 1.5 by 0.4 cm. and 1 by 0.4 by 0.3 cm. were transplanted into the retroperitoneal region and spleen of a young rhesus. The animal was used for a poliomyelitis experiment, and died of abscess of the brain. At

necropsy no evidence of Hodgkin's disease was found. Histologic examination showed scar tissue in the spleen at the site of transplantation.

Experiment 3.—Glands were removed from a man, about 37 years of age. This patient showed the first signs of Hodgkin's disease two years previously, and the nodes were removed at that time to confirm the diagnosis.

Fig. 4.—Low power reproduction of drawing of gland in Experiment 4. The part within the circle is represented in Figure 5.

In June, 1919, a gland was removed from the inguinal region, and a section 2 by 1 by 1 cm. was transplanted beneath the deep cervical fascia of a female chimpanzee about 6 years old.

Sections made from the gland (Fig. 3) were typical of Hodgkin's disease. Cultures made at the time of transplantation revealed diphtheroid bacilli in Petroff's culture medium and broth, and staphylococci in broth. The wound healed without infection. The animal died in November, 1919.

Experiment 4.—Glands were removed from a boy, aged 15 years, who gave a two years' history of swellings in the right side of the neck and right axilla.

In July, 1919, glands were removed from the cervical region and a slice of gland 3 by 2 by 1 cm. transplanted under the deep cervical fascia of a female chimpanzee about 6 years old.

The histologic picture was that of Hodgkin's disease (Figs. 4 and 5).

Anaerobic and aerobic cultures made from the gland at the time of transplantation revealed *Staphylococcus albus*, but the wound healed without infection. The animal was in perfect health two years after the experiment.

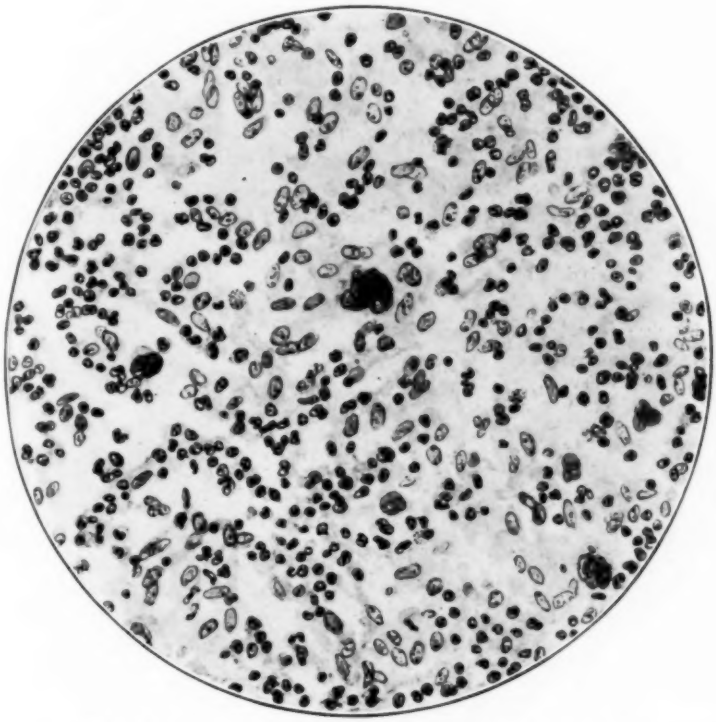

Fig. 5.—High power reproduction of field within circle in Figure 4.

COMMENT

The two rhesus monkeys were observed five and six months, respectively, and at necropsy showed no evidence of lymphomas.

The two chimpanzees were observed for about two years in our cages after the transplants were made and showed no external evidence of Hodgkin's disease. They were then used as exhibition animals in a circus. The one used in Experiment 3 died in November, 1921, the diagnosis by the veterinary surgeon being tuberculosis. Necropsy was not performed.

The second chimpanzee was taken ill about this time, the prominent symptoms being cough, loss of weight and fever. She died Feb. 5, 1922. Necropsy was performed forty-eight hours postmortem, the anatomic diagnosis being: Tuberculosis and edema of the lungs; tuberculosis of the cervical, tracheal and mesenteric lymph nodes; tuberculosis of the spleen, miliary and caseous; tuberculosis (?) of solitary follicles of the ileum; tuberculosis, miliary, of the liver. Microscopic examination was made of the lungs, lymph nodes, liver, spleen and intestines. The lungs presented an advanced degree of caseation, with the formation of tubercles without giant cells. The lymph nodes and spleen presented a similar picture. The liver presented marked fatty infiltration with pronounced postmortem change and a few small areas of necrosis, the nature of which was not determined. The kidneys also presented postmortem change, but no evidence of tuberculosis. On the mucosal surface of the ileum was a small ulceration with fibrosis and round cell infiltration.

Tuberculosis in chimpanzees is a rapidly fatal disease and there is little doubt that the infection took place after the animals left our cages. We have found no evidence that Hodgkin's disease has been produced in the rhesus monkeys and chimpanzees used in these experiments.

THE SIZE OF THE HEART IN PNEUMONIA

A TELEROENTGENOGRAPHIC STUDY, WITH OBSERVATIONS ON THE EFFECT OF DIGITALIS THERAPY *

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Precise information concerning the behavior of the heart in pneumonia is essential for the rational management of the circulation in this disease. Whether, in the course of acute pneumonitis, the cardiovascular system is functionally impaired, is still a matter of controversy. Direct methods for the estimation of myocardial function are still wanting. But alterations in the size of the heart furnish evidence, although indirect, of changes in the physical state of the myocardium, and in particular of variations in the length of heart muscle fiber. Such changes, as will be pointed out, have been shown by investigation to be associated with alterations in the volume output of the ventricles; and on the maintenance of ventricular volume output depends, in large measure, the efficiency of the circulation as a whole.

The present investigation was designed to obtain, by the roentgenographic method, at relatively frequent intervals, accurate records of the size of the heart in patients ill with pneumonia. The cardiac silhouette was outlined and measured according to a special technic, and an attempt has been made to estimate the significance of the changes observed. The effect of digitalis on the size of the heart has also been studied.

LITERATURE

It appears that Dietlen [1] is the only observer who has taken accurate records of the size of the heart in pneumonia throughout the course

TABLE 1.—*Size of Heart Throughout Disease in Dietlen's Case*

Day of disease....	2	3	5	6	7	11	12	14	19	21	24	25
Area, sq. cm.	123	123	133	135	134	123	122	122	122	122	117	116

of the disease. He made orthodiagrams of eleven cases of lobar pneumonia and found cardiac dilatation in four (36.4 per cent.). In two of these cases, the enlargement was slight and transitory; in the third

* From the Hospital of the Rockefeller Institute for Medical Research.

* A preliminary report of this work was read before the American Society for Clinical Investigation, May 9, 1921.

1. Dietlen, H.: Orthodiagraphische Beobachtungen über Veränderungen der Herzgrösse bei Infektionskrankheiten, bei exsudativer Perikarditis und paroxysmaler Tachykardie, nebst Bemerkungen über das roentgenologische Verhalten bei Pneumonie. München. med. Wchnschr. **55**:2077, 1908.

case it was somewhat greater. No figures are given. Measurements of the area are recorded in the fourth case, and are now reprinted, since the changes observed are comparable to those to be reported in this paper.

On the sixth and seventh days of the disease, the patient was very ill. He was first afebrile on the eleventh day. Dietlen remarks that dilatation was coincident with the severest period of the illness—"the dangerous time before crisis."

MATERIAL AND METHODS

Material.—Teleroentgenograms of the chest were made every second day, or at times as nearly approximating this interval as the condition of the patients warranted, of twenty-one cases of lobar pneumonia and eight cases of bronchopneumonia, during the acute stages of the disease and throughout convalescence in the hospital. Two hundred and eighty-four plates were taken and form the basis of this study. Three normal young men and one patient with fever due to acute bronchitis and pulmonary tuberculosis served as controls.

Method of Taking the Roentgenograms.—The exposures were made for one-half second, during the inspiratory phase of normal respiration, the subjects being in the recumbent position. The plates were at a distance of 2 meters from the anticathode of the roentgen-ray tube. The patient was instructed to breathe as quietly as possible and was unaware of the instant at which the picture was to be taken. In order to record graphically on the plate the phase of respiration in which the exposure was made, a lead strip was secured to the plateholder with adhesive plaster to indicate the neutral position of the vertically hanging lever of a Marey tambour, the lever being tipped with a solid knob of lead. The tambour was connected by means of rubber tubing with a Politzer bag, held in position in the right axilla of the patient by a linen binder, secured by fastening its tails. During respiration, the lever of the tambour swung on one side or the other of the neutral strip. The side to which the lever deviated during expiration was denoted by the letter *E* (Fig. 1). The pictures were obtained during inspiration in a majority of instances. Slight variations in the time of exposure were disregarded, as it has been shown, employing a similar technic, that the difference in the size of the heart during normal inspiration and expiration is so small as to be negligible.[2]

In order to verify the accuracy of anteroposterior alignment, a thin lead strip was placed over the spinous processes of the vertebrae, and

2. Cohn, A. E.: An Investigation of the Size of the Heart in Soldiers by the Teleroentgen Method, Arch. Int. Med. **25**:499 (May) 1920.

two acute angles of lead were secured anteriorly—one in the suprasternal notch, the other in the substernal angle. In later plates, the posterior lead strip was omitted, as the vertebral spines could be plainly seen in the negatives. Unclear or improperly aligned records were discarded.

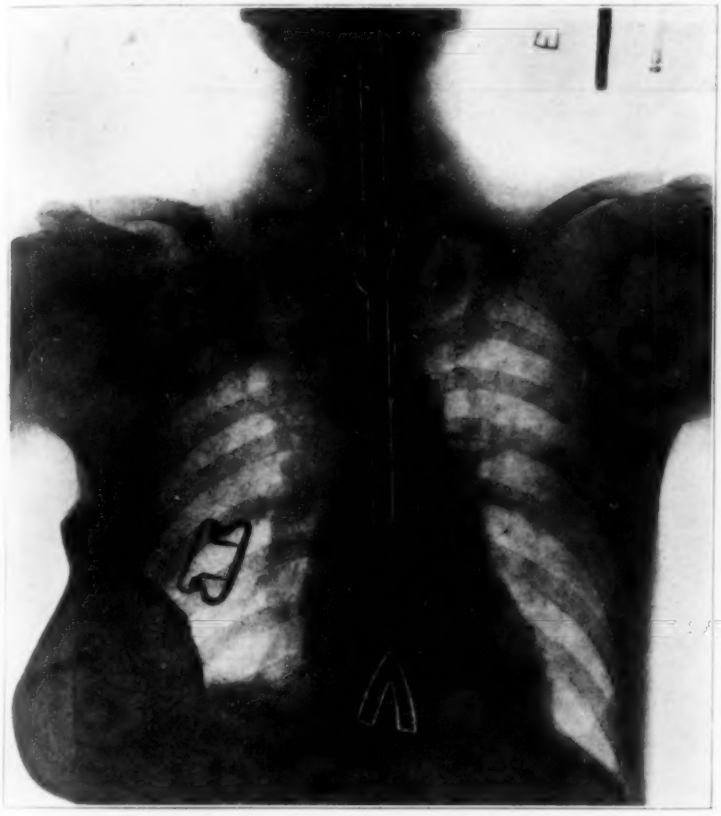

Fig. 1.—Teleroentgenogram, showing method of taking the plates.

A New Technic for Completing the Outline of the Cardiac Silhouette.—In the plates, the diastolic outline of the right and left borders and the midline were traced on paper. This made possible the measurement of transverse and long diameters. The angle of inclination of the heart—that is, the angle formed by the long diameter and a line drawn to the apex at right angles with the median line—was also recorded. Instead of completing the silhouette by arbitrarily joining

the ends of the lines defining the borders, a simple geometric construction was adopted, which rendered the procedure entirely objective (Fig. 2). In Figure 2, the heavy lines *a d* and *b e* represent, respectively, right and left borders, traced from the roentgenogram. Using the distance *a b* as a radius and *a* as a center, an arc was drawn. With the same radius, but with *b* as a center, another arc was drawn, intersecting the first at the point *c*. With *c* as center and *a b* again as a

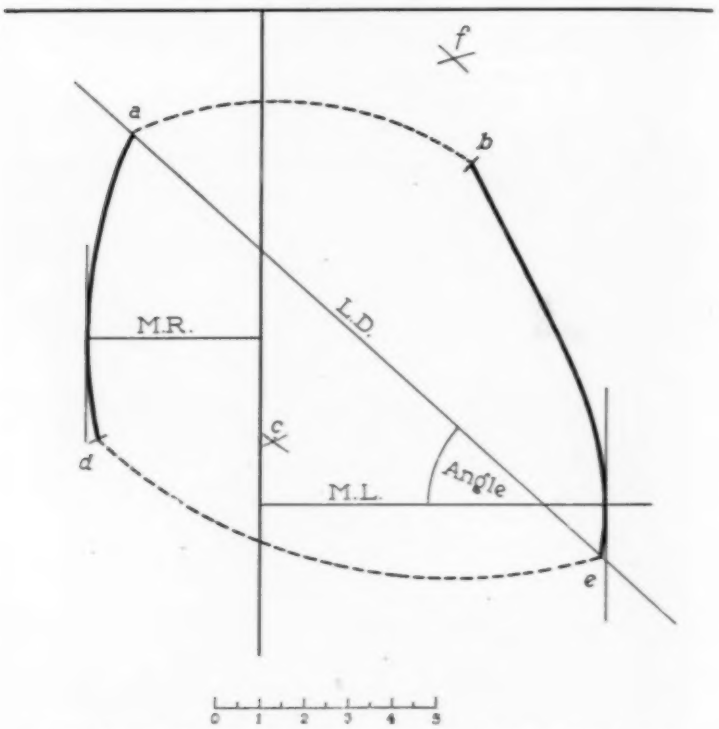

Fig. 2.—Construction of the cardiac silhouette, showing area, diameters and angle.

radius, the points *a* and *b* were joined. The arc *d e* was constructed in like fashion, employing the radius *d e* and the point *f* as center. The area so delineated was measured with a planimeter.

It is evident that if the distances *a b* and *d e* are constant, the areas bounded by these lines and their corresponding arcs must likewise be constant in value. Variations in these distances, on the other hand,

will be accompanied, in the same sense, by corresponding changes in the areas outlined. The subjective, arbitrary construction formerly employed may, therefore, properly be replaced by one which is objective even though arbitrary in its variations.

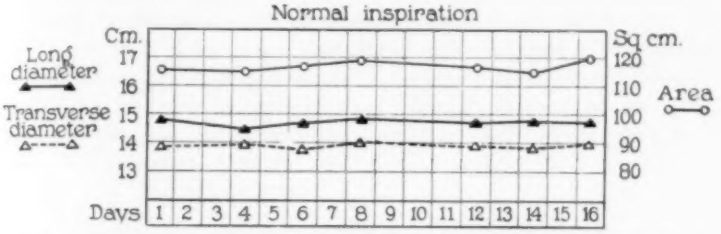

Fig. 3.—Graph of cardiac measurements in a normal young man, G. S., aged 17. Seven plates were made during a sixteen day period.

CONTROL SERIES

Variations in the cardiac measurements in the same person from day to day may be due either to the fact that significant changes in the size of the heart actually occur under ordinary conditions or to technical errors in the method of measurement. To obtain data on this point, roentgenograms were made, according to the technic described, of three normal young men who were workers in the laboratory. Plates were taken every second or third day until six or seven had been made

TABLE 2.—*Exposures Made During Normal Inspiration* *

	Horizontal Posture					
Date	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees
Feb. 18.....	5.4	7.9	13.3	14.0	111	35
Feb. 21.....	5.2	8.1	13.3	14.1	113	35
Feb. 23.....	5.7	7.7	13.4	14.1	113	37
Feb. 25.....	5.5	7.8	13.3	14.1	113	36
March 1.....	5.6	7.6	13.2	14.0	111	38
March 3.....	5.6	7.5	13.1	13.9	109	37
	Maximum Variations					
	0.5	0.5	0.3	0.2	4	3

* These roentgenograms were made of D. W. L., a man, aged 18 years, a normal person.

(Table 2). Measurements of these roentgenograms show that the maximum variation in transverse diameter was 0.6 cm., in long diameter 0.4 cm. and in area 8 square centimeters.[3]

3. Measurements of *M R*, *M L* and the angle of inclination are included in the tables for purposes of reference, but will not be alluded to in the discussion.

In order to ascertain the effect of fever and tachycardia on the size of the heart, measurements of the heart were made in a patient with acute bronchitis and pulmonary tuberculosis, but without signs of consolidation in the lungs. The maximum variation in transverse diameter was 0.7 cm., in long diameter 0.2 cm. and in area 1 sq. cm. That fever and tachycardia per se are not necessarily associated with a change in the size of the heart was later abundantly confirmed by observations on cases of pneumonia in which no alteration was noted (Fig. 4).

It seemed reasonable, on the basis of these findings, to regard as a significant change in the outline of the heart a variation of 1 cm. or more in one of the diameters, or of 10 sq. cm. or more in area. Usually,

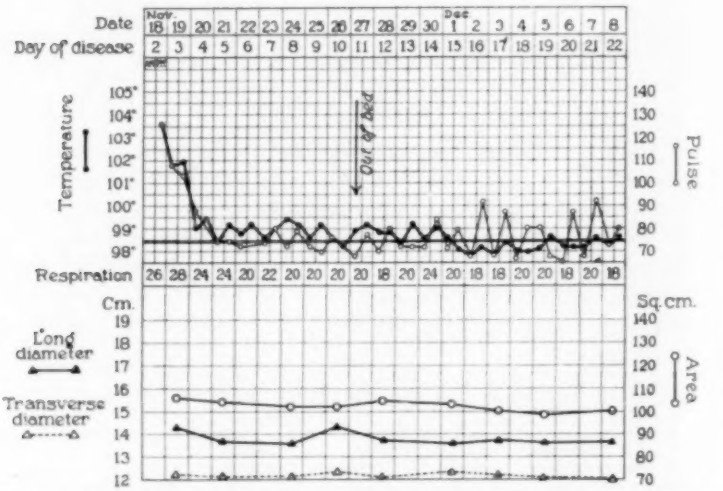

Fig. 4 (Case 24).—Clinical chart and cardiac measurements of a woman, A. J., aged 27, who had bronchopneumonia of the right lower lobe; pneumococcus, group IV.

when a change was observed, it took place in all measurements, and was of a greater order of magnitude than the minimal criteria established.

RESULTS IN PNEUMONIA

Lobar Pneumonia.—The twenty-one cases studied presented varying degrees of severity. Bacteriologic examination of the sputums showed the usual types of organisms (Table 3). The series is too small to permit of generalizations which take into account age and sex. Of the entire group, thirteen patients (61.9 per cent.) showed an increase in the size of the heart during the course of the illness. Eleven of the patients did not, however, receive digitalis; to ten this drug was given.

by mouth, in the form of digitan. Of the eleven patients not receiving digitalis, eight (72.7 per cent.) showed cardiac enlargement; of the ten receiving this drug, five (50 per cent.) showed cardiac enlargement

TABLE 3.—*Summary of Twenty-One Cases of Lobar Pneumonia Grouped According to Pneumococcus Types*

	Number of Cases	Percentage
Type I	12	57.1
Type II	2?	
Type IIA	1	15.1
Type III	1	5.1
Group IV	5	22.7
Type I.—12 Cases		
No change in heart size	3	25
Change	9	75
Cases Not Receiving Digitalis—7		
No change in heart size	1	14.3
Change	6	85.7
Cases Receiving Digitalis—5		
No change in heart size	2	40
Change	3	60
Type II and IIA—3 Cases		
No change in heart size (1 received digitalis)	2	66.7
Change	1	33.3
Type III—1 Case		
Change—Digitalis given		
Group IV—5 Cases		
No change in heart size	3	60
Change	2	40
Cases Not Receiving Digitalis—2		
No change in heart size	1	50
Change	1	50
Cases Receiving Digitalis—3		
No change in heart size	2	66.7
Change	1	33.3

TABLE 4.—*Summary (284 Plates)*

		Number of Cases	Percentage
Lobar Pneumonia—21 Cases			
No change in heart size		8	38.1
Change		13	61.9
(a) In all measurements	9		
(b) In long diameter and area only	4		
Cases Not Receiving Digitalis—11			
No change in heart size		3	27.3
Change		8	72.7
(a) In all measurements	6		
(b) In long diameter and area only	2		
Cases Receiving Digitalis—10			
No change in heart size		5	50
Change		5	50
(a) In all measurements	4		
(b) In long diameter and area only	1		
Bronchopneumonia—8 Cases			
No change in heart size		6	75
Change		2	25
(Change occurred in all measurements)			
Cases Not Receiving Digitalis or Strophanthin—6			
No change in heart size		4	66.7
Change		2	33.3
Cases Receiving Digitalis or Strophanthin—2			
No change in heart size		2	100
Change		0	

(Table 4). From these facts it appears that: (1) in about 62 per cent. of these cases of lobar pneumonia, cardiac dilatation occurred during the course of the disease; (2) cardiac dilatation occurred less frequently in the patients who received digitalis than in those who did not.

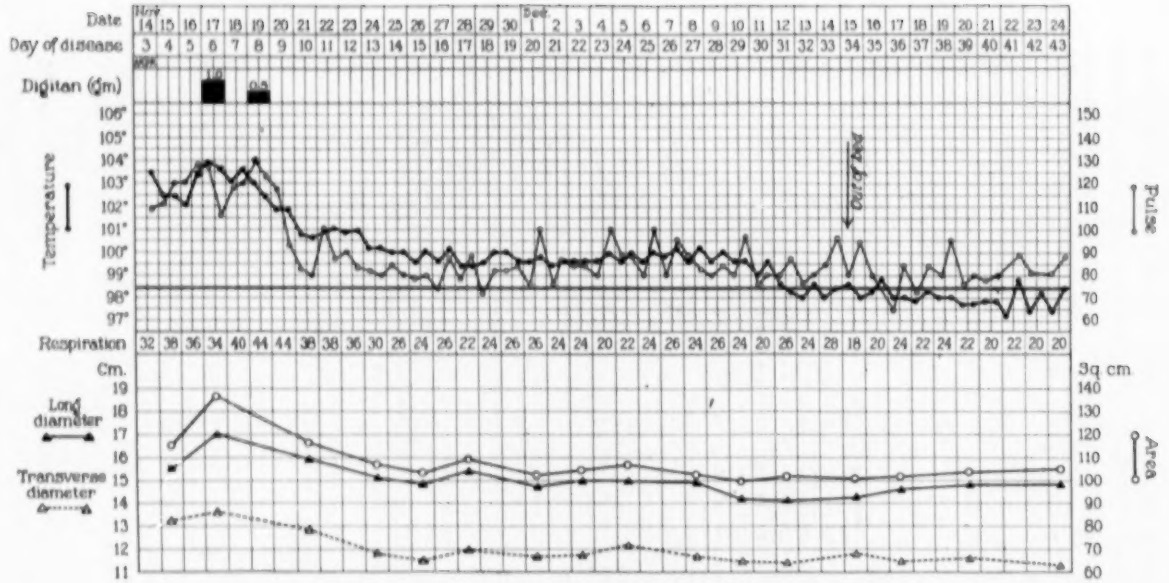

Fig. 5 (Case 15).—Clinical chart and cardiac measurement of a man, aged 29, with pneumonia of the right upper, middle and lower lobes and of the left lower lobe; pneumococcus, Type III.

The order of magnitude of the change is of interest (Table 5). In the patients not receiving digitalis, the increase in transverse diameter was from 4.5 to 15.4 per cent. (an average of 9.3 per cent.); in long diameter from 4.4 to 13.5 per cent. (an average of 8.2 per cent.; in area from 11.6 to 27.1 per cent. (an average of 16.5 per cent.). In the digitalized patients who showed enlargement, the increase in transverse diameter was from 3.6 to 19.2 per cent. (an average of 11.0 per cent.); in long diameter, from 2.6 to 19.7 per cent. (an average of

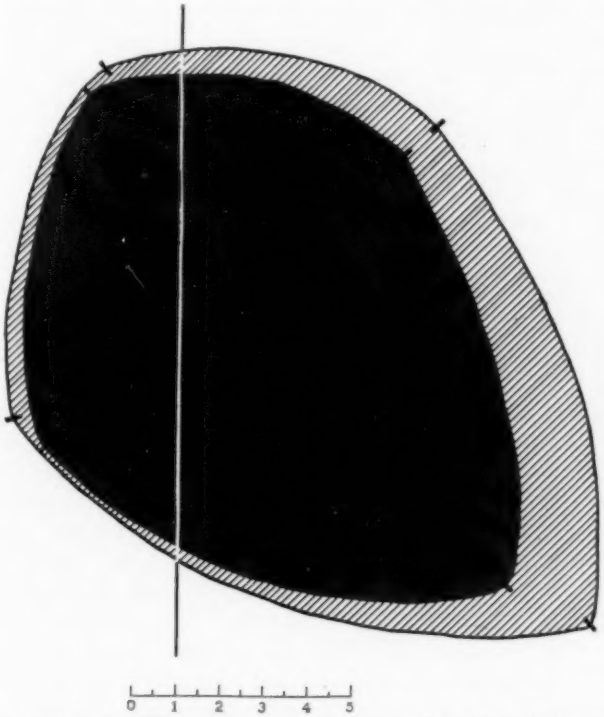

Fig. 6 (Case 15).—Silhouettes showing extremes of variation in heart size.

10.2 per cent.); in area from 11.1 to 37.3 per cent. (an average of 18.5 per cent.). The differences in the two groups are not striking. The averages in the second group are increased by the figures obtained from a patient with Type III pneumococcus infection involving the entire right lung and the left lower lobe. In this man, critically ill, the transverse diameter fell from 13.6 cm. at the height of the disease to 11.4 cm. during convalescence, the long diameter from 17.0 to 14.2 cm., the area from 136 square cm. to 99 square cm. (Figs. 5 and 6).

TABLE 5.—*Summary of Twenty-One Cases of Lobar Pneumonia and Eight Cases of Bronchopneumonia, Showing Relation of Changes in Heart Size to Digitalis Therapy*

Case No. Name; Age	Bacteriology	Lobes Involved	Heart Size*	Maximal Percentage Change: Area	Maximal Percentage Change: Transverse Diameter	Maximal Percentage Change: Long Diameter	Digitalis or Strophanthin	Total Amount Given	Day of Disease Drug Begun	Serum
1. E. M. 52	Pneumococcus I Bacillus influenzae	L. L.	+	16.2	9.0	9.7	0	.....	...	+
2. M. P. 29	Pneumococcus I	L. L.	+	27.1	12.2	12.5	0	.....	...	+
3. S. P. 36	Pneumococcus I Bacillus influenzae	L. L.	+	19.5	7.1	10.5	0	.....	...	+
4. H. D. 39	Pneumococcus I	L. L.	+	11.6	4.5	6.5	0	.....	...	+
5. P. K. 19	Pneumococcus I Bacillus influenzae	L. L.	+	12.3	5.8	4.2	0	.....	...	+
6. L. M. 21	Pneumococcus I Bacillus influenzae	R. L., L. L.	+	12.5	12.3	7.1	0	.....	...	+
7. F. T. 29	Pneumococcus IV Bacillus influenzae	R. L.	+	15.0	8.5	11.4	0	.....	...	..
8. T. M. 47	Pneumococcus IIA	R. L.	+	18.5	15.4	4.4	0	.....	...	..
9. J. K. 18	Pneumococcus II	R. L., L. L.	0	0	0	0	0	.....	...	..
10. J. S. 28	Pneumococcus IV	L. L.	0	0	0	0	0	.....	...	..
11. S. B. 13	Pneumococcus I Bacillus influenzae	R. U.	0	0	0	0	0	.....	...	0
12. J. C. 30	Pneumococcus I	R. L.	+	11.1	3.6	2.6	+	0.6 gm.	5	+
13. P. O'M. 25	Pneumococcus I	R. U., R. M., R. L.	+	18.4	8.9	8.8	+	0.8 gm.	4	+
14. E. D. 39	Pneumococcus I	R. U., L. L.	+	14.7	13.0	10.4	+	1.5 gm.	4	+
15. A. T. 29	Pneumococcus III	R. U., R. M., R. L., L. L.	+	37.3	19.2	19.7	+	1.5 gm.	6	..
16. F. L. 32	Pneumococcus IV	L. L.	+	11.2	10.2	9.7	+	1.5 gm.	4	..
17. V. P. 26	Pneumococcus I	R. L.	0	0	0	0	+	1.5 gm.	5	+
18. M. L. 34	Pneumococcus I Bacillus influenzae	L. L.	0	0	0	0	+	0.9 gm.	2	+
19. L. W. 16	Pneumococcus II Bacillus influenzae	R. L.	0	0	0	0	+	1.8 gm.	2	..
20. A. R. 37	Pneumococcus IV	R. U.	0	0	0	0	+	0.9 gm.	6	..
21. R. L. 34	Pneumococcus IV Bacillus influenzae	L. L.	0	0	0	0	+	1.0 gm.	2	..
				Bronchopneumonia						
22. M. Q. 39	Pneumococcus IV Bacillus influenzae	Dif. bilat.	+	17.1	3.7	5.2	0	.....	...	..
23. E. S. 56	Pneumococcus IV	L. L.	+	29.8	12.0	20.1	0	.....	...	..
24. A. J. 27	Pneumococcus IV	R. L.	0	0	0	0	0	.....	...	..
25. G. B. 13	Streptococcus hemolyticus	R. L.	0	0	0	0	0	.....	...	..
26. C. G.* 35	Streptococcus hemolyticus, Bacillus influenzae	Dif. bilat.	—	—	—	—	0	.....	...	..
27. M. K. 19	Pneumococcus IV	R. L.	0	0	0	0	Dig.	1.0 gm.	6	..
28. A. D. P.† 34	Staphylococcus aureus, Bacillus influenzae	R. L.	0	0	0	0	Stroph.	0.7 mg.	8	..
29. G. E.‡ ?	Pneumococcus IV Bacillus influenzae	Dif. bilat.	0	0	0	0	Stroph.	0.5 mg.	21	..

* Died.
† Patient had mitral stenosis.
‡ Died; strophanthin given late.

The correspondence in this case between the size of the heart and the clinical condition is striking. Digitalis was not administered until the sixth day of illness, at a time when the patient's life hung in the balance. The temperature from this day on fell by lysis and the heart decreased in size, reaching a constant level on the twentieth day of disease.

As a rule, the increase in heart size was gradual, often reaching its maximum at the height of the disease, but sometimes after the subsidence of fever. The return to a constant level was also gradual, at times lagging behind the fall in temperature and pulse rate (Figs. 7 and 8). In a number of cases, there was marked postfebrile decrease in size, the heart at this time being smaller than during later convalescence (Figs. 9 and 10). In two instances, one patient receiving digitalis (Case 16), the other (Case 7) not receiving this drug, the heart was distinctly larger during convalescence than during the height of the illness. In both cases there was pronounced bradycardia during the convalescent period.

In the thirteen patients showing increase in the size of the heart, the change was observed in all measurements in nine; in long diameter and area only, in four. The transverse diameter was accordingly the least reliable index of variation. The greatest percentage variation occurred in the area. It is impossible to attempt to determine from the tracings which chamber or chambers of the heart participated in the enlargement. For the method employed measures only a portion of the heart, in a single plane.

Bronchopneumonia.—Eight cases were studied (Tables 4 and 5). Of these, a change in the size of the cardiac silhouette occurred in two (25 per cent.), and was observed in all measurements. In one patient with diffuse, bilateral, streptococcus pneumonia, of whom plates were made until three days before death, there was seen a progressive diminution in the size of the heart (Case 26). No observations were made during the last three days. He received no digitalis.

Of the eight cases, one, a boy of 19 years, received digitalis, beginning on the sixth day of the disease; another, who had mitral stenosis, received 0.7 mg. of strophanthin intravenously on the eighth day of illness. Neither of these patients showed a change in the size of the heart. The drugs were given late in the course of the pneumonia so that their influence on the behavior of the heart is a matter of doubt.

In brief, it is apparent that cardiac dilatation is less frequently encountered in bronchopneumonia (25 per cent.) than in lobar pneumonia (61.9 per cent.). When it occurs, as will be seen from Table 5 and from Figures 7 and 8, the change is comparable in degree and

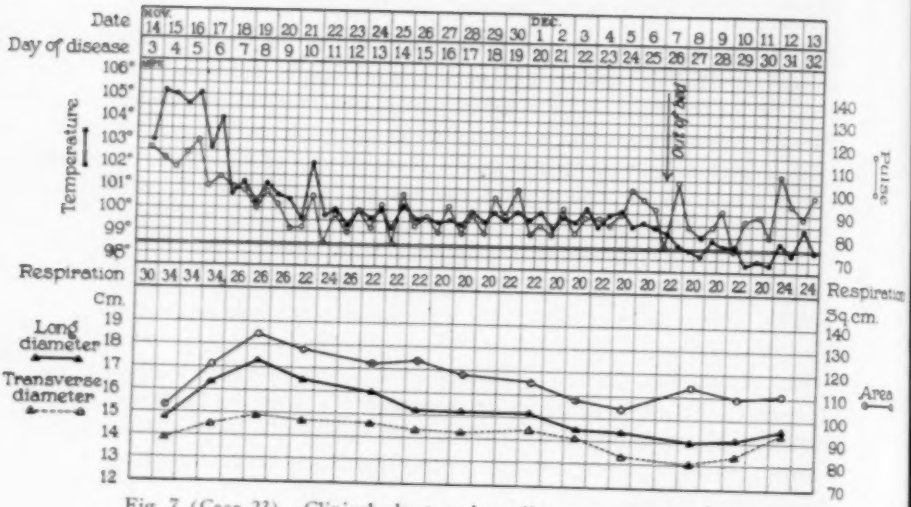

Fig. 7 (Case 23).—Clinical chart and cardiac measurements of a woman, aged 55, with bronchopneumonia of the left lower lobe; pneumococcus, Group IV.

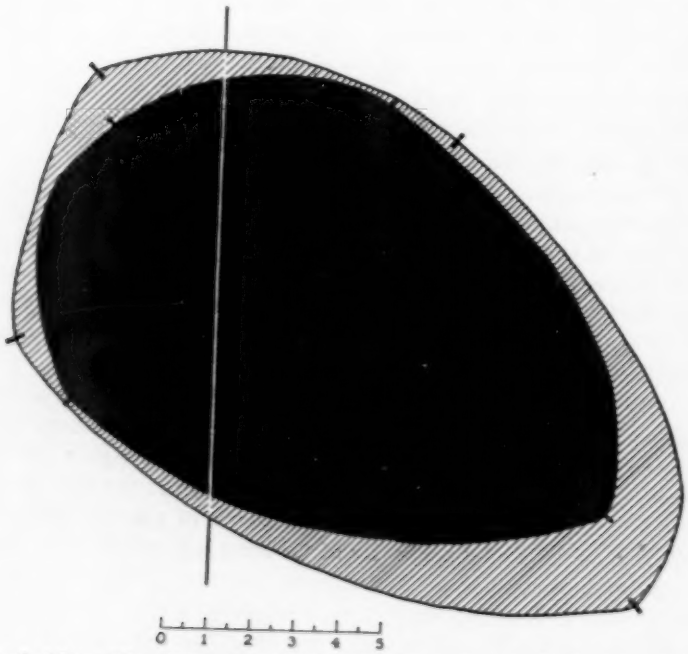

Fig. 8 (Case 23).—Silhouettes showing extremes of variation in heart size.

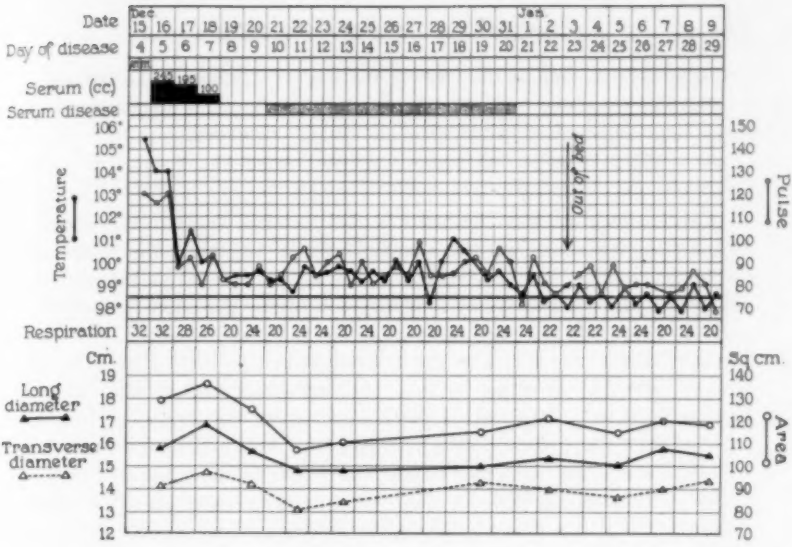

Fig. 9 (Case 2).—Clinical chart and cardiac measurements of a woman, aged 29, with lobar pneumonia of the left lower lobe; pneumococcus, Type I.

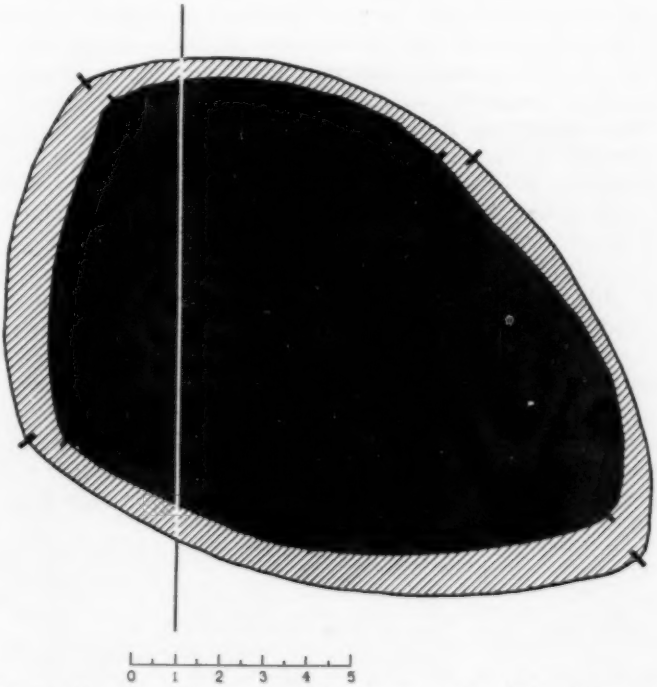

Fig. 10 (Case 2).—Silhouettes showing extremes of variation in heart size.

character to that seen in the latter condition. Evidence of the influence of digitalis is scant, but it tends to support the view that when the drug is given, cardiac dilatation is less likely to occur.

DISCUSSION

Cardiac Dilatation.—The heart is able to adapt itself in remarkable fashion to variations in the demands made on it in the form of mechanical work. The mechanism of this adaptation has been made the subject of particular study by Starling,[4] employing the heart-lung preparation. He found that any increase in the work of the heart, however caused, whether by a rise in the arterial pressure or by a more rapid venous inflow, is attended by a corresponding increase in the volume of the ventricles. And, within physiologic limits, the larger the volume of the heart, the greater is the energy of its contractions as measured by systolic output. The law of the heart is thus the same as the law of muscular tissue in general, that "the energy of contraction, however measured, is a function of the length of the muscle fibre." Up to a physiologic optimum, cardiac dilatation is an adaptive, compensatory mechanism favorable to the maintenance of an adequate circulation. In a healthy person, to accomplish this adaptation may be only a temporary necessity; for the circulation improves as a result of augmented cardiac efficiency, the cardiac tone itself increases, and the heart gradually returns to a normal volume even though doing increased work. But, when the heart is fatigued or diseased, the secondary improvement fails to appear, and the myocardium remains dilated over the period of increased work. If the work is prolonged, dilatation may become permanent, and may even exceed the optimum length of muscle fiber. If this occurs, the muscle must contract at so great a mechanical disadvantage that heart failure ensues.

Anatomic lesions in the heart in pneumonia are, according to a majority of investigators, infrequent and, relatively speaking, insignificant.[5] In the pneumonias associated with influenza in soldiers, Stone,[6] however, reports parenchymatous, fatty and hyaline degeneration or evidence of inflammatory reaction in the heart muscle in 79.3 per cent. of the microscopic sections from thirty-four necropsies of cases of lobar pneumonia and in 59.4 per cent. of the sections from thirty-seven necropsies of cases of bronchopneumonia. It is of interest to recall, in this connection, the greater frequency, in the present study,

4. Starling, E. H.: The Linacre Lecture on the Law of the Heart, Longmans, Green & Co., London, 1918.

5. Cohn, A. E., and Jamieson, R. A.: The Action of Digitalis in Pneumonia, J. Exper. M. **25**:65, 1917. (This article, on p. 73, contains a review of the literature.)

6. Stone, W. J.: The Heart Muscle Changes in Pneumonia, with Remarks on Digitalis Therapy, Am. J. M. Sc. **163**:659, 1922.

of cardiac dilatation in lobar pneumonia (61.9 per cent.) than in bronchopneumonia (25 per cent.). Aside from structural change, there are present in pneumonia at least three conditions which are concerned in throwing an added burden of work on the heart. These are: (1) impairment of the circulation in the pneumonic lung; (2) toxemia, and (3) anoxemia.

(1) Impairment of the Circulation in the Lung: In a study of injected lungs from patients dying of lobar pneumonia, Kline and Winternitz[7] and, more recently, Gross[8] have demonstrated varying degrees of vascular obliteration, depending in extent on the stage of pulmonary consolidation. In a lung described by Gross, in which the two upper lobes were consolidated, the lower lobe showed tremendous dilatation of the vessels with massive injection. The capillaries appeared to be two or three times their normal caliber, and the entire lobe presented a striking picture of compensatory arterial dilatation. In the upper lobe, there was some preservation of the circulation, but the injected vessels were narrowed. The middle lobe showed general lack of injection; only several large, compressed branches were apparent, and these ended abruptly. Thus, when exudation is at its height, there is almost complete vascular obliteration. With the arterial bed in the lung markedly diminished in area, the pressure in the pulmonary artery is increased, and the right ventricle is obliged to contract against a heightened resistance.[9] In bronchopneumonia this factor is probably of less significance than in lobar pneumonia.

(2) Toxemia: The heart muscle in pneumonia is fed by blood containing bacterial toxins and perhaps also products of autolysis yielded by the exudate in the lung alveoli. Pertinent experimental evidence on the effect of these poisons on the heart is afforded by the work, on dogs, of Newburgh and Porter.[10] They found that the heart muscle is not functionally impaired in pneumonia, since the pneumonic ventricle beats normally as soon as it is fed with normal blood; that pneumonic blood, suddenly fed to normal heart muscle, lowers its efficiency, lessening the duration and the force of contraction; but that the heart muscle in pneumonia, exposed gradually to the action of the poison, largely adjusts itself to the poisoned food. Clinical observations lend support to these findings.

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7. Kline, B. S., and Winternitz, M. C.: Studies Upon Experimental Pneumonia in Rabbits. VIII. Intra Vitam Staining in Experimental Pneumonia and the Circulation in the Pneumonic Lung, J. Exper. M. **21**:311, 1915.

8. Gross, L.: Preliminary Report on the Reconstruction of the Circulation of the Liver, Placenta and Lung in Health and Disease, Canad. M. A. J. **9**:632, 1919.

9. Wiggers, C. J.: Circulatory Failure, J. A. M. A. **70**:508 (Feb. 23) 1918.

10. Newburgh, L. H., and Porter, W. T.: The Heart Muscle in Pneumonia, J. Exper. M. **22**:123, 1915.

(3) Anoxemia: High arterial unsaturation, with its accompanying clinical manifestation, cyanosis, is a frequent occurrence in both lobar and bronchopneumonia, due, in large measure, according to Stadie,[11] to an impairment in the function of the respiratory surface of the lungs. The greater the lung involvement, the greater is the anoxemia. Especially is this so when the pneumonic process extends throughout the lungs, as is the case when there are many patches of bronchopneumonia, with accompanying bronchitis and edema. That the circulation as a whole may suffer from oxygen want is evident from Stadie's observation that, after administration of oxygen in 60 per cent. concentration in a closed chamber, to a moribund and pulseless patient, the heart rate fell from 160 to 120, the pulse returned to the radial artery, the color became pink, and there was remarkable clinical improvement.[12] Other, less striking observations support this view. No records of the size of the heart were made in his cases.

It seems clear, then, that for the reasons given, and perhaps others, the heart may be called on to do more than its usual quota of mechanical work in pneumonia, and that, in certain instances, it responds to the increased demands made on it by dilatation, with resultant lengthening of its muscle fibers. Whether the physiologic optimum of lengthening is ever exceeded, remains an open question. Certainly the signs of heart failure, in the ordinary sense, are conspicuous by their absence. The venous pressure, taken by the method of Hooker, was, moreover, in a number of our cases, within normal limits. The mechanism of adaptation, as has been pointed out, is a gradual one, sometimes reaching its maximum after the height of the disease has been passed. The return of the heart to a smaller and constant volume is likewise a gradual process, and, in that sense, may be regarded as indicating recovery from a functional injury.

The Therapeutic Use of Digitalis.—Clinicians are agreed that when auricular fibrillation or flutter occurs in the course of pneumonia, the prompt exhibition of digitalis in adequate doses exerts not merely a beneficial effect but is at times responsible for the saving of life. In the presence of normal (sinus) rhythm, there is still doubt as to its value. Cohn and Jamieson[5] have pointed out that in patients with pneumonia the usual digitalis effects on auriculoventricular conduction and on the T-wave of the electrocardiogram may be obtained; and that whatever beneficial action the drug has on the function of the normally beating, nonfebrile heart may also be expected from its use in pneumonia.

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11. Stadie, W. C.: The Oxygen of the Arterial and Venous Blood in Pneumonia and Its Relation to Cyanosis, J. Exper. M. **30**:215, 1919.

12. Stadie, W. C.: The Treatment of Anoxemia in Pneumonia in an Oxygen Chamber, J. Exper. M. **25**:337, 1922.

Another consideration, however, leads to the suggestion that digitalis may be a rationally useful therapeutic measure. Cohn and I [13] have shown, in dogs, that digitalis, in amounts comparable to the therapeutic dose in man, increases the contractile power of the ventricular muscle, and by so doing augments systolic volume output. At a time when the increase in output occurs, there are usually characteristic changes in the T-wave of the electrocardiogram.

From the facts presented in this paper, it is evident that the heart muscle in pneumonia may attempt, by calling on a reserve mechanism, dilatation, to augment systolic output. In a relatively large number of the patients who received digitalis, the heart did not increase in size. It, therefore, seems reasonable to infer that when the ventricle is stimulated to increased force of contraction by digitalis, the compensatory mechanism of dilatation, in some instances at least, is not called into play. To that extent, the reserve force of the heart is not encroached on. It is, therefore, logical to suggest the use of early and adequate digitalis therapy in pneumonia, in the belief that it may exert a beneficial effect not only in the presence of auricular fibrillation and flutter, but also when the normal rhythm prevails.

SUMMARY

1. A teleroentgenographic study was made of twenty-one cases of lobar pneumonia and eight cases of bronchopneumonia, employing a special technic in making the plates and a new method in completing the outline of the cardiac silhouette.

2. In lobar pneumonia, cardiac dilatation occurred in 61.9 per cent. of the cases. Dilatation was less frequently observed in patients who received digitalis (50 per cent.) than in those to whom the drug was not given (72.7 per cent.).

3. In bronchopneumonia, cardiac dilatation was less frequent than in lobar pneumonia, having been observed in 25 per cent. of the cases. The two patients in this group who received digitalis showed no dilatation.

4. The heart muscle in pneumonia may attempt, by lengthening its muscle fibers, to augument systolic output. Digitalis, in therapeutic doses, increases the contractile power of the ventricles. On the basis of these facts, early and adequate digitalis therapy is suggested in pneumonia, in the belief that the drug may exert a beneficial effect, not only in the presence of auricular fibrillation and flutter, but also when the normal rhythm prevails.

13. Cohn, A. E., and Levy, R. L.: The Effect of Therapeutic Doses of Digitalis on the Contraction of Heart Muscle, Proc. Soc. Exper. Biol. & Med. **17**:160, 1920.

TABLE 6.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data								Clinical Data			
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Serum, C.c.	Serum, Disease	Maximum Temperature	Maximum Pulse
1/ 2/20	5	4151	2.8	9.2	12.0	13.3	89	25	190	..	104.5	128
1/ 5/20	8	4158	2.9	9.0	11.9	13.5	93	36	....	..	100.1	80
1/ 7/20	10	4164	2.4	9.3	11.7	12.6	84	29	....	..	100.1	80
1/ 9/20	12	4171	2.9	8.1	11.0	12.3	81	32	....	..	100.0	84
1/14/20	17	4184	3.2	8.3	11.5	12.4	82	31	....	..	99.0	86
1/16/20	19	4193	3.2	8.3	11.5	12.7	83	32	....	..	99.6	84
1/19/20	22	4204	3.3	8.7	12.0	13.3	88	33	....	..	99.6	84
1/21/20	24	4215	3.5	7.8	11.3	12.7	80	33	....	..	99.3	96
1/23/20	26	4227	3.6	8.4	12.0	13.0	86	31	....	+	99.3	90
1/26/20	29	4237	3.3	8.4	11.7	13.0	82	33	....	+	99.4	85
2/ 8/21	Returned	4997	4.0	8.4	12.8	13.1	85	28	....	..	....	86

* Case 1, E. M., a man, aged 52 years, had pneumonia of the left lower lobe. Pneumococcus, Type I, and B. influenzae were present. The patient recovered.

TABLE 7.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data								Clinical Data			
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Serum, C.c.	Serum, Disease	Maximum Temperature	Maximum Pulse
12/15/19	4	....	...	...	....	....	...	..	....	..	105.4	124
12/16/19	5	4104	4.5	9.6	14.1	15.8	129	40	245	..	105.2	128
12/17/19	6	....	...	....	....	....	...	..	195	..	102.0	108
12/18/19	7	4113	4.0	10.7	14.7	16.8	136	40	100	..	101.5	100
12/20/19	9	4120	3.6	10.6	14.2	15.6	125	39	....	..	99.6	88
12/21/19	10	....	...	....	....	....	...	..	....	+	99.2	88
12/22/19	11	4122	2.9	10.2	13.1	14.8	107	40	....	+	99.7	96
12/24/19	13	4132	3.0	10.4	13.4	14.8	110	38	....	+	99.7	98
12/30/19	19	4140	3.0	11.2	14.2	15.0	115	35	....	+	99.5	92
1/ 2/20	22	4149	4.2	9.7	13.9	15.3	120	37	....	..	99.0	90
1/ 3/20	23	....	...	....	....	....	...	..	....	..	99.6	84
1/ 5/20	25	4156	3.9	9.8	13.7	15.0	115	39	....	..	99.6	86
1/ 7/20	27	4162	3.5	10.4	13.9	15.7	120	41	....	..	98.4	86
1/ 9/20	29	4168	4.4	9.9	14.3	15.4	118	38	....	..	98.6	90
2/ 4/21	Returned	4978	5.0	8.3	13.3	14.3	113	41	....	..	....	..

* Case 2, M. F., a woman, aged 29 years, had pneumonia of the left lower lobe. Pneumococcus, Type I, was present. The patient recovered.

TABLE 8.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data								Clinical Data			
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Serum, C.c.	Serum, Disease	Maximum Temperature	Maximum Pulse
11/25/19	4	....	...	....	....	....	...	..	....	..	103.8	120
11/26/19	5	4008	4.5	11.3	15.8	16.0	145	32	300	..	103.8	120
11/27/19	6	....	...	....	....	....	...	..	195	..	102.2	108
11/28/19	7	4014	4.7	10.7	15.4	16.0	141	38	....	..	100.2	80
12/ 1/19	10	4028	3.8	12.7	16.5	16.7	147	32	....	..	99.2	78
12/ 2/19	11	....	...	....	....	....	...	..	....	+	99.2	78
12/ 3/19	12	4042	4.1	11.3	15.4	15.1	123	33	....	+	99.6	99
12/ 5/19	14	4061	4.1	11.4	15.6	14.9	124	34	....	+	99.0	78
12/ 8/19	17	4069	2.4	11.9	15.3	14.9	134	29	....	+	99.4	72
12/10/19	19	4083	4.5	11.1	15.6	15.7	..	29	....	+	99.4	86
12/12/19	21	4090	4.4	11.1	15.5	15.3	126	34	....	..	99.2	78
12/15/19	24	4100	4.2	11.3	15.5	15.8	132	34	....	..	99.0	78
2/ 2/21	Returned	4963	5.6	9.0	14.6	15.5	128	44	....	..	....	..

* Case 3, S. P., a man, aged 36 years, had pneumonia of the left lower lobe. Pneumococcus, Type I, and B. influenzae were present. The patient recovered.

TABLE 9.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data			
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Serum, C.c.	Serum, Disease	Maximum Temperature	Maximum Pulse
4/28/21	4	....	...	....	....	....	...	..	90	..	106.0	115
4/29/21	5	5423	5.0	11.1	16.1	15.5	144	22	200	..	106.8	122
4/30/21	6	....	...	....	....	....	...	..	100	..	101.6	85
5/ 2/21	8	5433	5.1	11.1	16.2	16.2	144	24	...	..	99.5	80
5/ 4/21	10	5453	5.6	9.9	15.5	15.3	131	26	...	..	99.0	72
5/ 6/21	12	5467	5.5	10.1	15.6	15.2	130	26	...	..	98.6	76
5/ 9/21	15	5476	5.4	10.3	15.7	15.3	129	25	...	+	99.4	68
5/11/21	17	5483	5.2	10.6	15.8	15.3	132	23	...	+	98.8	72
5/13/21	19	5494	5.5	10.1	15.6	15.4	131	24	...	..	99.2	74
5/16/21	22	5500	4.6	11.1	15.7	15.4	133	22	...	..	98.8	68
5/18/21	24	5512	5.3	10.5	15.8	15.3	129	21	...	..	99.4	68
5/20/21	26	5518	5.4	10.4	15.8	15.3	131	23	...	..	99.2	72

* Case 4, H. D., a man, aged 39 years, had pneumonia of the left lower lobe. Pneumococcus, Type I, was present. The patient recovered.

TABLE 10.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data			
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Serum, C.c.	Serum, Disease	Maximum Temperature	Maximum Pulse
11/24/19	4	....	...	...	....	....	...	..	...	..	105.0	134
11/25/19	5	4000	5.0	8.7	13.7	14.3	114	37	190	..	105.6	132
11/26/19	6	4009	4.7	9.2	13.9	14.4	112	35	195	..	106.0	130
11/28/19	8	4015	4.7	9.5	14.2	14.8	125	39	...	..	99.4	68
11/30/19	10	....	...	...	....	....	...	..	....	+	99.0	60
12/ 1/19	11	4029	4.6	10.0	14.0	14.8	127	35	....	..	99.1	54
12/ 3/19	13	4040	4.8	9.3	14.1	14.5	120	36	....	..	99.6	72
12/ 5/19	15	4060	3.9	10.1	14.0	13.7	114	30	....	..	99.4	74
12/ 6/19	16	....	...	....	....	....	...	..	....	+	99.0	68
12/ 8/19	18	4068	4.9	8.9	13.8	14.2	113	34	....	..	99.0	70
12/10/19	20	4082	4.4	9.8	14.2	14.7	120	33	....	..	99.1	72
12/12/19	22	4091	5.1	9.2	14.3	15.0	128	38	....	..	99.2	64
12/15/19	25	4099	4.3	10.2	14.5	14.7	125	32	....	..	99.4	72
2/ 7/21	Returned	4991	4.9	9.1	14.0	14.1	115	36	....	..	....	..

* Case 5, P. K., a man, aged 19 years, had pneumonia of the left lower lobe. Pneumococcus, Type I, and B. influenzae were present. The patient recovered.

TABLE 11.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data			
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Serum, C.c.	Serum, Disease	Maximum Temperature	Maximum Pulse
12/ 3/19	4	....	...	....	....	....	...	..	75	..	104.8	124
12/ 4/19	5	4060	5.3	10.4	15.7	16.5	144	36	195	..	105.0	112
12/ 5/19	6	....	...	....	....	....	...	..	290	..	103.0	102
12/ 6/19	7	....	...	....	....	....	...	..	265	..	101.6	96
12/ 8/19	9	4071	4.0	11.3	15.2	16.8	132	32	...	+	100.8	86
12/10/19	11	4084	4.9	10.1	15.0	15.9	131	36	...	+	101.6	88
12/12/19	13	4095	4.2	10.6	14.9	15.4	128	31	...	+	102.4	100
12/15/19	16	4101	4.4	10.8	15.2	16.0	131	32	...	..	99.6	90
12/17/19	18	4110	4.9	10.2	15.2	16.4	130	34	...	..	99.4	76
12/19/19	20	4116	4.9	10.0	14.9	15.6	129	34	...	..	99.6	78
12/22/19	23	4123	4.1	10.8	14.9	16.1	130	35	...	..	99.2	88
12/24/19	25	4135	3.9	11.1	15.0	15.9	133	33	...	..	99.6	88
12/30/19	31	4143	4.8	10.2	15.0	16.4	138	36	...	..	99.5	88
2/ 7/21	Returned	4990	4.8	10.5	15.3	15.6	141	34	...	..	....	..

* Case 6, L. M., a man, aged 21 years, had pneumonia of the right and left lower lobes. Pneumococcus, Type I, and B. influenzae were present. The patient recovered.

TABLE 12.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data	
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Maximum Temperature	Maximum Pulse
3/ 9/21	6	....	...	...	....	....	...	..	103.9	100
3/10/21	7	5155	4.0	9.7	13.7	14.1	109	36	104.6	92
3/12/21	9	5167	4.6	8.5	13.1	13.9	108	40	100.0	88
3/14/21	11	5169	5.7	7.5	13.2	13.4	101	38	100.0	72
3/16/21	13	5185	5.4	7.5	12.9	13.1	100	39	100.1	72
3/18/21	15	5196	5.0	7.4	12.0	13.3	101	38	99.6	72
3/21/21	18	5211	5.5	8.0	12.5	13.7	106	38	99.4	84
3/23/21	20	5230	5.5	8.5	14.0	14.1	110	35	99.4	72
3/25/21	22	5249	5.0	8.9	13.9	14.1	112	34	99.6	84
3/28/21	25	5262	5.5	8.4	13.9	14.6	115	33	99.2	76
3/30/21	27	5275	4.8	9.0	13.8	14.3	113	33	99.4	72

* Case 7, F. T., a man, aged 29 years, had pneumonia of the right lower lobe. Pneumococcus, Group IV, and B. influenzae were present. The patient recovered.

TABLE 13.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data	
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Maximum Temperature	Maximum Pulse
12/ 4/19	5	....	...	....	....	....	...	..	103.8	96
12/ 5/19	6	4059	4.2	11.6	15.8	16.5	134	31	103.0	96
12/ 8/19	9	4070	3.7	11.0	14.7	16.8	127	37	99.5	72
12/10/19	11	4081	4.4	9.1	13.5	15.9	117	39	99.1	84
12/12/19	13	4092	5.0	8.7	13.7	15.8	113	37	99.3	80
12/15/19	16	4098	5.2	8.9	14.1	15.5	114	35	99.0	78
12/17/19	18	4109	4.8	9.5	14.3	15.9	123	33	99.0	84
12/18/18	19	....	...	....	....	....	...	..	99.0	78
12/19/19	20	4118	4.5	10.0	14.6	15.8	119	26	99.0	84
12/22/19	23	4125	4.5	9.4	13.9	15.4	120	34	99.0	80
12/24/19	25	4134	3.8	10.5	14.3	15.6	122	32	99.2	82
12/30/19	31	4144	3.8	10.8	14.7	15.7	121	27	99.2	80

* Case 8, T. M., a man, aged 47 years, had pneumonia of the right lower lobe. Pneumococcus, Type IIA, was present. The patient recovered.

TABLE 14.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data	
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Maximum Temperature	Maximum Pulse
4/12/21	6	....	...	....	....	....	...	..	104.1	148
4/13/21	7	5328	3.4	12.1	15.5	15.6	127	26	102.9	102
4/18/21	12	5336	3.7	12.0	15.7	15.9	130	25	99.9	72
4/20/21	14	5382	4.4	10.8	15.2	15.6	120	29	99.4	82
4/22/21	16	5391	4.5	11.1	15.6	15.7	126	26	99.9	80
4/25/21	18	5400	5.3	10.3	15.6	15.8	123	28	99.6	84
4/27/21	20	5406	5.5	10.1	15.6	16.0	125	30	99.2	82
4/29/21	22	5417	5.2	9.9	15.1	15.5	118	28	99.4	82
5/ 2/21	26	5431	5.6	9.9	15.5	15.5	122	26	100.0	88
5/ 4/21	28	5451	5.5	9.9	15.4	15.8	128	29	99.6	86
5/ 6/21	30	5464	5.5	9.8	15.5	15.6	124	32	100.0	80
5/ 9/21	33	5474	5.4	10.5	15.9	16.0	130	30	100.0	80

* Case 9, J. K., a youth, aged 18 years, had pneumonia of the right and left lower lobes. Pneumococcus, Type II, was present. The patient recovered.

TABLE 15.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data	
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Maximum Temperature	Maximum Pulse
3/28/21	5	....	...	...	....	....	...	..	105.0	126
3/29/21	6	5270	4.7	8.6	13.3	14.4	105	39	104.4	108
3/31/21	8	5280	4.6	8.8	13.4	14.3	106	40	99.2	72
4/ 2/21	10	5294	3.9	9.7	13.4	14.3	104	36	99.2	80
4/ 5/21	13	5307	4.6	8.3	12.9	13.7	100	38	99.6	76
4/ 7/21	15	5311	4.4	8.4	12.8	13.5	101	38	99.4	72
4/ 9/21	17	5319	3.9	9.2	13.1	13.8	101	36	99.9	80
4/11/21	19	5326	4.1	9.1	13.2	14.0	108	41	100.0	86
4/13/21	21	5336	4.2	8.4	12.6	13.5	101	39	100.1	74
4/15/21	23	5352	4.5	8.0	12.5	14.1	101	42	100.0	88
4/18/21	26	5364	4.2	8.9	13.1	14.2	104	38	99.6	84
4/20/21	28	5381	4.3	8.5	12.8	14.0	101	37	100.0	90
4/22/21	30	5390	4.3	8.7	13.0	14.1	104	36	100.0	90
4/25/21	33	5398	4.7	8.2	12.9	14.3	103	41	100.1	92
4/27/21	35	5405	4.2	8.3	12.5	13.9	101	39	99.8	88

* Case 10, J. S., a man, aged 28, had pneumonia of the left lower lobe. Pneumococcus, Group IV, was present. The patient recovered.

TABLE 16.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data	
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Maximum Temperature	Maximum Pulse
2/14/21	6	....	...	...	....	....	..	..	101.2	116
2/15/21	7	5037	3.5	8.8	12.3	13.1	79	27	101.0	100
2/17/21	9	5051	3.8	8.8	12.6	13.3	82	27	98.8	84
2/18/21	10	5060	4.2	8.4	12.6	13.2	81	26	98.8	84
2/21/21	13	5072	4.0	8.5	12.5	13.0	81	25	99.6	80
2/22/21	14	....	...	...	....	....	..	..	99.0	96
2/23/21	15	5080	3.7	8.7	12.4	12.7	77	24	99.6	84
2/25/21	17	5087	3.9	8.2	12.1	12.5	76	25	99.6	96
2/28/21	20	5101	3.3	8.8	12.1	12.4	77	25	99.4	100

* Case 11, S. B., a youth aged 13 years, had pneumonia of the right upper lobe. Pneumococcus, Type I, and B. influenzae were present. The patient recovered.

TABLE 17.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data				
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Trans. Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Serum, C.c.	Serum Disease	Digitan, Gm.	Maximum Temperature	Maximum Pulse
2/ 6/21	4	....	...	...	....	....	...	..	...	...	...	104.4	120
2/ 7/21	5	5004	5.1	9.0	14.1	15.4	120	40	200	...	0.2	105.7	156
2/ 8/21	6	....	...	...	....	....	...	..	100	...	0.4	103.4	128
2/11/21	9	5024	5.3	8.6	13.9	15.2	119	41	...	...	...	99.3	98
2/14/21	12	5034	5.2	8.4	13.6	15.0	110	39	...	+	...	99.2	92
2/16/21	14	5046	4.8	8.9	13.7	15.2	114	40	...	+	...	99.4	100
2/19/21	17	5062	4.4	9.6	14.0	15.6	114	38	...	+	...	99.3	82
2/21/21	19	5070	4.8	9.4	14.2	15.6	120	38	...	+	...	99.6	84
2/23/21	21	5082	5.6	8.1	13.7	14.6	109	38	...	+	...	99.8	94
2/25/21	24	5088	5.5	8.6	14.1	15.5	121	38	...	...	...	98.5	88
2/28/21	27	5099	6.1	7.6	13.7	15.1	110	37	...	...	...	99.3	78
3/ 3/21	29	5126	5.3	8.3	13.6	15.0	108	38	...	...	...	99.0	96
3/ 7/21	33	5144	5.3	8.2	13.5	15.0	113	35	...	...	...	99.6	80

* Case 12, J. C., a man, aged 30 years, had pneumonia of the right lower lobe. Pneumococcus, Type I, was present. The patient recovered.

TABLE 18.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data								Clinical Data				
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Serum, C.c.	Serum Disease	Digitan, Gm.	Maximum Temperature	Maximum Pulse
3/22/21	4	5225	4.1	11.7	15.8	17.4	136	35	180	...	0.4	104.4	106
3/23/21	5	....	...	....	....	....	...	..	90	....	0.4	102.6	92
3/24/21	6	5243	4.9	11.0	15.9	17.5	141	34	....	....	....	100.6	66
3/26/21	8	5257	5.1	10.3	15.4	17.5	139	39	....	....	....	99.7	80
3/28/21	10	5268	4.8	10.9	15.7	17.0	136	33	....	+	....	99.4	69
3/30/21	12	5272	4.4	10.2	14.6	15.9	119	32	....	+	....	101.6	92
4/ 1/21	14	5286	4.6	10.1	14.7	16.2	124	35	....	+	....	99.2	80
4/ 4/21	17	5296	4.9	10.1	15.0	16.5	127	33	....	....	....	99.4	76
4/ 6/21	19	5310	4.7	10.7	15.2	16.3	129	30	....	....	....	99.2	64
4/ 8/21	21	5317	4.5	10.4	14.9	16.0	122	30	....	....	....	99.1	84
4/11/21	24	5327	4.7	10.8	15.5	16.8	124	32	....	....	....	99.1	82
4/13/21	26	5337	4.2	11.8	16.0	16.7	128	28	....	....	....	99.0	84

* Case 13, P. O'M., a man, aged 25 years, had pneumonia of the right upper, middle and lower lobes. Pneumococcus, Type I, was present. The patient recovered.

TABLE 19.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data								Clinical Data				
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Serum, C.c.	Serum Disease	Digitan, Gm.	Maximum Temperature	Maximum Pulse
11/11/21	4	....	...	...	....	....	....	..	....	...	1.0	104.0	112
11/12/21	5	5796	5.5	8.3	13.8	15.0	110	39	200	...	0.5	103.6	96
11/13/21	6	....	...	...	....	....	....	..	200	....	....	102.0	100
11/14/21	7	5800	6.0	7.3	13.3	14.5	106	39	100	....	....	101.2	108
11/16/21	9	5810	6.1	7.9	14.0	14.8	112	36	....	....	....	101.2	82
11/18/21	11	5816	5.6	7.8	13.4	14.6	109	39	....	....	....	100.8	92
11/19/21	12	....	...	...	....	....	....	..	....	+	....	102.6	96
11/22/21	15	5824	5.8	7.2	13.0	14.4	106	39	....	+	....	102.4	104
11/23/21	16	5828	5.4	8.5	13.9	15.4	115	39	....	+	....	102.8	116
11/25/21	18	5835	5.4	8.7	14.1	15.5	116	38	....	+	....	103.5	120
11/28/21	21	5839	5.7	8.4	14.1	15.9	118	41	....	....	....	103.0	120
11/30/21	23	5853	5.1	8.9	14.0	15.9	117	39	....	....	....	101.8	102
12/13/21	36	5907	5.3	9.1	14.4	15.3	113	35	....	....	....	99.4	90
12/15/21	38	5913	5.9	8.8	14.7	15.8	114	35	....	....	....	99.1	82
12/19/21	42	5923	4.9	9.2	14.1	15.3	107	35	....	....	....	99.6	88
12/21/21	44	5928	5.1	8.4	13.5	15.2	103	37	....	....	....	100.0	84

* Case 14, E. D., a man, aged 39 years, had pneumonia of the left lower and right upper lobes. Pneumococcus, Type I, was present. The patient recovered.

TABLE 20.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data			
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Digitan, Gm.	Maximum Temperature	Maximum Pulse
11/14/19	3	....	...	...	....	....	....	..	...	104.2	118
11/15/19	4	3902	3.8	9.4	13.2	15.5	115	41	...	104.4	130
11/17/19	6	3906	4.0	9.6	13.6	17.0	126	48	1.0	103.9	127
11/19/19	8	....	...	...	....	....	....	..	0.5	103.0	128
11/21/19	10	3965	3.7	9.1	12.8	15.9	116	47	...	101.6	98
11/24/19	13	3994	4.0	7.7	11.7	15.1	107	50	...	101.4	82
11/26/19	15	4005	3.5	8.0	11.5	14.8	103	48	...	100.6	80
11/28/19	17	4013	3.2	8.7	11.9	15.4	109	46	...	100.2	90
12/ 1/19	20	4027	2.9	8.7	11.6	14.7	102	52	...	100.3	100
12/ 3/19	22	4041	3.0	8.7	11.7	15.0	104	45	...	100.2	86
12/ 5/19	24	4052	3.1	9.0	12.1	14.9	106	44	...	100.3	88
12/ 8/19	27	4067	3.5	8.1	11.6	14.9	102	46	...	100.2	86
12/10/19	29	4078	3.8	7.6	11.4	14.2	99	46	...	100.0	96
12/12/19	31	4089	3.2	8.2	11.4	14.1	101	45	...	99.0	88
12/15/19	34	4095	3.7	8.0	11.7	14.2	100	45	...	98.5	80
12/17/19	36	4107	3.6	7.9	11.4	14.6	101	49	...	98.0	84
12/20/19	39	4119	3.8	7.7	11.5	14.8	103	48	...	98.5	80
12/24/19	43	4131	4.0	7.2	11.2	14.8	104	50	...	98.5	88
2/ 9/21	Returned	5003	4.3	7.6	11.9	13.6	102	45	...	....	..

* Case 15, A. T., a man, aged 29 years, had pneumonia of the right upper, middle and lower lobes and of the left lower lobe. Pneumococcus, Type III, was present. The patient recovered.

TABLE 21.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data		
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Digitan, Gm.	Maximum Temperature	Maximum Pulse
10/12/21	3	....	...	...	....	....	...	..	...	104.4	98
10/13/21	4	5681	5.3	9.8	15.1	15.0	108	27	1.0	102.6	90
10/14/21	5	....	...	...	....	....	...	..	0.5	106.2	96
10/15/21	6	5689	5.0	9.7	14.7	14.4	107	28	...	102.4	88
10/18/21	9	5695	5.6	10.1	15.7	15.1	115	24	...	100.2	76
10/20/21	11	5704	5.0	11.1	16.1	15.4	115	22	...	99.8	60
10/22/21	13	5714	5.5	10.7	16.2	15.8	119	23	...	99.6	68
10/24/21	15	5719	4.9	11.0	15.9	15.7	114	24	...	99.7	68
10/26/21	17	5728	4.5	11.3	15.8	15.5	114	21	...	99.6	74

* Case 16, F. L., a man, aged 32 years, had pneumonia of the left lower lobe and chronic heroin poisoning. Pneumococcus, Group IV, was present. The patient recovered from pneumonia but the second condition was unimproved.

TABLE 22.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data				
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Trans. Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Serum, C.c.	Serum Disease	Digitan, Gm.	Maximum Temperature	Maximum Pulse
2/23/21	4	....	...	...	....	....	...	..	...	...	...	104.6	120
2/24/21	5	5085	5.1	7.5	12.6	12.9	99	32	90	...	0.3	105.0	112
2/25/21	6	....	...	...	....	....	...	..	180	...	0.7	104.2	104
2/26/21	7	5097	5.4	7.2	12.6	13.0	100	34	...	...	0.5	100.6	96
3/ 1/21	10	5112	5.0	7.1	12.1	12.7	97	30	...	...	...	100.3	80
3/ 3/21	12	5127	5.0	6.7	11.7	12.3	94	38	...	...	...	99.9	92
3/ 4/21	13	....	...	...	....	....	...	..	...	+	...	100.4	92
3/ 5/21	14	5137	5.5	6.5	12.0	12.5	95	37	...	+	...	101.9	96
3/ 7/21	16	5143	5.4	6.6	12.0	12.2	96	34	...	...	...	100.6	100
3/ 9/21	18	5152	5.5	6.3	11.8	12.4	95	37	...	...	...	100.6	88
3/11/21	20	5159	5.5	6.5	12.0	12.6	99	38	. .	...	...	99.3	88
3/14/21	23	5170	5.2	7.0	12.2	12.9	100	35	...	...	...	100.0	84
3/16/21	25	5186	5.4	6.6	12.0	12.3	96	37	...	...	...	100.0	92
3/18/21	27	5196	5.4	6.9	12.3	12.7	96	34	...	...	...	99.2	90
3/21/21	30	5212	5.8	6.2	12.0	12.8	100	42	...	...	...	99.6	88
3/23/21	32	5231	5.2	6.7	11.9	13.0	101	39	...	...	...	100.0	90

* Case 17, V. P., a man, aged 26 years, had pneumonia of the right lower lobe and otitis media of the left ear. Pneumococcus, Type I, was recovered from the sputum; hemolytic streptococci and staphylococci were present in the discharge from the ear. The patient recovered.

TABLE 23.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data				
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Trans. Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Serum, C.c.	Serum Disease	Digitan, Gm.	Maximum Temperature	Maximum Pulse
1/ 4/22	2	....	...	...	....	....	...	..	...	...	0.8	104.0	120
1/ 5/22	3	5085	5.6	7.7	13.3	13.9	100	39	100	...	...	105.3	128
1/ 6/22	4	6006	5.5	8.0	13.5	14.2	100	44	...	...	0.1	101.4	118
1/ 9/22	7	6013	5.0	7.6	12.6	14.0	106	42	...	...	...	99.6	92
1/11/22	9	6035	4.7	7.6	12.3	13.8	98	40	...	+†	...	99.4	80
1/14/22	12	6042	4.2	8.4	12.6	13.7	101	37	...	...	...	99.1	88
1/16/22	14	6052	3.6	9.1	12.7	14.1	103	34	...	...	...	99.8	78
1/18/22	16	6058	4.0	8.0	12.0	13.9	99	38	...	...	...	99.1	92
1/20/22	18	6062	4.2	8.5	12.7	13.8	100	38	...	...	...	99.4	80
1/23/22	21	6068	5.6	9.3	12.9	13.9	101	37	...	...	...	99.4	80
1/25/22	23	6109	4.9	8.4	13.3	14.0	104	35	...	...	...	99.2	88

* Case 18, M. L., a woman, aged 34, had pneumonia of the left lower lobe. Pneumococcus, Type I, and B. influenzae were present. The patient recovered.

† Serum disease began on the ninth day and continued through the eleventh day.

TABLE 24.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data		
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Digitan, Gm.	Maximum Temperature	Maximum Pulse
10/21/21	2	....	...	...	....	....	...	..	0.4	105.2	138
10/22/21	3	5716	4.6	8.6	13.2	13.9	108	35	1.0	104.0	136
10/23/21	4	....	...	...	....	....	...	..	0.4	102.8	116
10/24/21	5	5718	4.3	9.3	13.6	14.2	114	32	...	101.1	100
10/26/21	7	5727	4.6	8.9	13.5	13.9	113	29	...	99.1	80
10/28/21	9	5744	5.3	8.3	13.6	13.9	112	30	..	98.8	76
10/31/21	12	5755	4.9	8.2	13.1	13.3	107	35	...	99.4	78
11/ 2/21	14	5761	4.6	8.7	13.3	13.7	111	35	...	99.5	92
11/ 4/21	16	5771	4.7	8.4	13.1	13.4	109	34	...	99.0	84

* Case 19, L. W., a youth, aged 16 years, had pneumonia of the right lower lobe. Pneumococcus, Type II, and B. influenzae were present. The patient recovered.

TABLE 25.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data		
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Digitan, Gm.	Maximum Temperature	Maximum Pulse
12/27/21	5	5961	4.5	9.1	13.6	14.4	111	33	...	104.5	106
12/28/21	6	....	...	...	....	....	...	..	0.4	104.2	98
12/29/21	7	....	...	...	....	....	...	..	0.5	103.4	84
12/30/21	8	5995	4.9	9.2	14.1	14.3	108	30	...	99.6	72
1/ 3/22	12	5970	5.2	8.8	14.0	14.9	112	34	...	98.6	66
1/ 5/22	14	5986	5.2	8.6	13.9	14.5	108	34	...	99.0	72
1/ 7/22	16	6004	5.1	9.7	14.8	15.2	114	28	...	98.9	64
1/ 9/22	18	6010	4.8	9.1	13.9	14.4	104	32	...	99.0	82
1/11/22	20	6033	4.6	9.8	14.4	14.7	111	29	...	99.4	72
1/14/22	23	6038	5.0	9.3	14.3	14.8	110	31	...	99.4	74

* Case 20, A. R., a man, aged 37 years, had pneumonia of the right upper lobe. Pneumococcus, Group IV, was present. The patient recovered.

TABLE 26.—*Findings in a Case of Lobar Pneumonia* *

		Roentgenographic Data							Clinical Data		
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Digitan, Gm.	Maximum Temperature	Maximum Pulse
1/ 1/22	2	....	...	....	....	....	...	..	0.6	102.6	116
1/ 2/22	3	....	...	....	....	....	...	..	0.4	100.0	89
1/ 3/22	4	5971	4.0	10.0	14.0	14.8	114	42	...	99.5	65
1/ 5/22	6	5987	3.9	10.4	14.2	14.9	118	36	...	99.4	65
1/ 6/22	7	6005	4.1	10.2	14.4	14.7	116	31	...	98.4	65
1/ 9/22	10	6011	4.3	9.9	14.2	14.8	113	35	...	99.0	68
1/11/22	12	6054	4.2	10.3	14.5	15.0	120	33	...	98.2	76
1/16/22	17	6069	4.1	10.3	14.4	14.7	115	36	...	98.4	65
1/18/22	19	6064	4.0	10.1	14.1	14.6	116	33	...	98.4	70

* Case 21, R. L., a man, aged 34 years, had pneumonia of the left lower lobe. Pneumococcus, Group IV, and B. influenzae were present. The patient recovered.

TABLE 27.—*Findings in a Case of Bronchopneumonia* *

		Roentgenographic Data							Clinical Data	
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Maximum Temperature	Maximum Pulse
12/ 3/19	8	....	...	....	....	....	...	..	103.4	100
12/ 4/19	9	4048	5.4	11.4	16.8	18.0	142	28	102.6	102
12/ 6/19	11	4063	5.4	11.4	16.8	17.9	146	26	101.6	94
12/ 8/19	13	4072	5.3	12.1	17.4	18.4	150	26	101.0	84
12/12/19	17	4093	5.1	11.7	16.8	17.9	143	26	101.0	88
12/15/19	20	4102	4.3	11.9	16.2	17.0	128	24	100.5	88
12/17/19	22	4111	5.5	11.7	17.2	17.7	139	18	100.6	80
12/19/19	24	4117	4.0	13.0	17.0	17.8	138	21	100.7	80
12/22/19	27	4124	4.0	13.3	17.3	18.3	139	21	100.7	80
12/24/19	29	4136	4.3	12.4	16.7	17.3	134	20	98.8	78
12/30/19	35	4142	4.4	12.8	17.2	17.8	137	19	98.6	88
1/ 2/20	38	4150	4.8	12.7	17.5	18.1	135	21	97.8	76
1/ 5/20	41	4157	4.4	12.0	16.4	17.2	137	22	98.6	84
2/ 2/21	Returned	4966	5.7	12.2	17.9	18.7	146	23	....	..

* Case 22, M. Q., a man, aged 39 years, had diffuse bilateral bronchopneumonia. Pneumococcus, Group IV, and B. influenzae were present. The patient recovered.

TABLE 28.—*Findings in a Case of Bronchopneumonia* *

		Roentgenographic Data							Clinical Data	
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Maximum Temperature	Maximum Pulse
11/14/19	3	....	...	....	....	....	...	..	103.0	116
11/15/19	4	3959	3.7	10.2	13.9	14.8	103	39	105.4	112
11/17/19	6	3965	4.0	10.5	14.5	16.4	121	44	104.1	110
11/19/19	8	3976	4.6	10.3	14.9	17.3	135	42	101.0	98
11/21/19	10	3980	4.1	10.6	14.7	16.5	128	41	102.0	96
11/24/19	13	3993	4.1	10.5	14.6	16.0	122	59	100.3	92
11/26/19	15	4005	3.8	10.6	14.4	15.2	124	37	100.5	88
11/28/19	17	4018	3.6	10.7	14.3	15.2	118	37	100.4	88
12/ 1/19	20	4025	3.4	11.0	14.4	15.2	115	35	100.0	84
12/ 3/19	22	4039	4.0	10.1	14.1	14.5	108	38	100.6	96
12/ 5/19	24	4057	4.1	9.2	13.3	14.4	104	37	100.2	100
12/ 8/19	27	4065	4.3	8.8	13.1	14.0	114	43	99.0	98
12/10/19	29	4079	3.5	9.9	13.4	14.2	109	37	98.7	100
12/12/19	31	4088	4.0	10.4	14.4	14.5	111	35	98.7	106

* Case 23, E. S., a woman, aged 55 years, had bronchopneumonia of the left lower lobe. Pneumococcus, Group IV, was present. The patient recovered.

TABLE 29.—*Findings in a Case of Bronchopneumonia* *

		Roentgenographic Data							Clinical Data	
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Maximum Temperature	Maximum Pulse
11/18/19	2	....	...	...	....	....	...	..	104.0	126
11/19/19	3	3972	4.0	8.2	12.2	14.2	106	50	102.4	110
11/21/19	5	3982	4.1	8.0	12.1	13.6	104	47	100.0	84
11/24/19	8	3991	3.9	8.2	12.1	13.5	102	47	100.0	80
11/26/19	10	4006	3.8	8.5	12.3	14.3	102	49	99.4	80
11/27/19	11	....	...	...	....	....	...	..	100.0	78
11/28/19	12	4016	3.8	8.3	12.1	13.7	104	45	99.6	80
12/ 1/19	15	4026	4.0	8.3	12.3	13.5	103	46	98.6	80
12/ 3/19	17	4037	3.6	8.6	12.2	13.7	100	46	99.3	88
12/ 5/19	19	4056	3.7	8.4	12.1	13.6	98	45	98.6	80
12/ 8/19	22	4066	3.4	8.6	12.0	13.6	100	42	98.8	80

* Case 24, A. J., a woman, aged 27 years, had bronchopneumonia of the right lower lobe. Pneumococcus, Group IV, was present. The patient recovered.

TABLE 30.—*Findings in a Case of Bronchopneumonia* *

		Roentgenographic Data							Clinical Data	
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Maximum Temperature	Maximum Pulse
2/ 3/21	5	4976	4.0	8.5	12.5	13.0	101	33	101.0	90
2/ 9/21	11	5006	4.0	8.4	12.4	12.8	97	35	99.2	70
2/11/21	13	5021	4.1	8.1	12.2	12.7	97	30	99.6	94
2/14/21	16	5063	4.0	8.3	12.3	12.8	98	32	98.3	70

* Case 25, G. B., a girl, aged 13 years, had bronchopneumonia of the right lower lobe. Streptococcus hemolyticus was present. The patient recovered.

TABLE 31.—*Findings in a Case of Bronchopneumonia* *

		Roentgenographic Data							Clinical Data	
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Maximum Temperature	Maximum Pulse
1/ 9/20	7	....	...	...	....	....	...	..	103.2	100
1/10/20	8	4173	5.2	9.0	14.2	14.5	118	30	102.8	92
1/12/20	10	4177	5.6	8.5	14.1	14.7	113	31	103.5	116
1/14/20	12	4186	5.0	9.2	14.2	14.5	113	30	103.0	120
1/16/20	14	4194	4.9	9.2	14.1	14.5	112	29	102.8	116
1/19/20	17	4205	5.6	7.3	12.9	13.6	105	36	105.8	128

* Case 26, C. G., a man, aged 35, had diffuse bilateral bronchopneumonia. Hemolytic streptococcus and B. influenzae were present. The patient died.

TABLE 32.—*Findings in a Case of Bronchopneumonia* *

		Roentgenographic Data							Clinical Data		
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Digitan, Gm.	Maximum Temperature	Maximum Pulse
11/23/21	5	....	...	...	....	....	...	..	...	105.8	110
11/24/21	6	....	...	...	....	....	...	..	0.6	104.9	108
11/25/21	7	5834	4.6	8.3	12.9	14.5	107	43	0.4	105.2	114
11/29/21	11	5847	4.6	8.1	12.7	14.2	106	42	...	99.0	108
12/ 1/21	13	5865	4.8	9.1	13.4	15.0	109	40	...	100.4	88
12/ 5/21	17	5876	4.7	8.1	12.8	14.9	106	44	...	98.5	80
12/ 7/21	19	5880	4.5	8.4	12.9	14.9	106	42	...	99.4	86
12/ 9/21	21	5891	4.6	8.6	13.2	14.8	109	41	...	99.4	86
12/12/21	24	5899	4.0	8.8	12.8	14.8	105	43	...	99.6	88
12/14/21	26	5909	4.6	8.8	13.4	15.1	109	41	...	99.8	88
12/19/21	31	5932	4.2	8.6	12.8	14.5	104	42	...	99.2	90
12/21/21	33	5936	4.1	9.1	13.2	14.9	107	40	...	99.5	94

* Case 27, M. K., a youth, aged 19 years, had bronchopneumonia of the right lower lobe. Pneumococcus, Group IV, was present. The patient recovered.

TABLE 33.—*Findings in a Case of Bronchopneumonia* *

		Roentgenographic Data							Clinical Data		
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Strophanthin, Gm.	Maximum Temperature	Maximum Pulse
1/ 6/20	7	4161	4.4	7.2	11.6	12.9	89	37	...	104.0	84
1/ 7/20	8	4166	3.7	7.6	11.3	12.9	89	38	0.7	104.2	86
1/ 9/20	10	4172	4.2	7.2	11.4	12.5	85	36	...	100.5	70
1/12/20	13	4175	4.4	7.3	11.7	13.1	91	36	...	99.3	66
1/14/20	15	4183	4.3	7.6	11.9	13.0	93	35	...	98.6	70
1/16/20	17	4191	4.5	7.2	11.7	13.0	90	38	...	98.6	66
1/19/20	20	4199	4.3	7.2	11.5	12.7	87	35	...	98.8	72
1/21/20	22	4213	4.1	7.4	11.6	12.8	89	36	...	98.8	79
1/23/20	25	4226	4.5	7.0	11.5	12.8	89	36	...	99.3	88

* Case 28, A. D. P., a woman, aged 34 years, had bronchopneumonia of the right lower lobe, chronic endocarditis and mitral stenosis. Staphylococcus aureus and albus and B. influenzae were present. The patient recovered.

TABLE 34.—*Findings of a Case of Bronchopneumonia* *

		Roentgenographic Data							Clinical Data		
Date	Day of Disease	Plate No.	Maximum Right, Cm.	Maximum Left, Cm.	Transverse Diameter Cm.	Long Diameter Cm.	Area, Sq. Cm.	Angle, Degrees	Strophanthin, Gm.	Maximum Temperature	Maximum Pulse
11/23/19	7	....	...	...	....	....	..	..	...	102.8	124
11/24/19	8	3995	4.1	5.9	10.1	10.9	81	50	...	104.6	140
11/26/19	10	4006	4.1	5.7	9.8	10.7	77	51	...	103.3	135
11/28/19	12	4017	4.0	6.1	10.1	10.7	79	49	...	102.8	136
12/ 7/19	21	....	...	...	....	....	..	..	0.2	102.8	170
12/10/19	24	....	...	...	....	....	..	..	0.3	101.4	176

* Case 29, G. E., a boy, aged 7 years, had diffuse bilateral bronchopneumonia. Pneumococcus, Group IV, and B. influenzae were present. The patient died.

DEFINITION OF HEMOLYTIC STREPTOCOCCUS PARASITISM IN THE UPPER AIR PASSAGES OF HEALTHY PEOPLE *

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The study of an epidemic or of an outbreak of certain acute infectious diseases can perhaps best be approached from the standpoint of deviation from average or normal conditions. Such a mode of attack seems specially applicable to those infections caused by bacteria which may be harbored by carriers, and which are constantly present, at least to a certain extent, in the community; and the question which presents itself is why the apparent balance between parasite and host becomes upset, with a consequent spread of organisms and production of disease. The problem is tremendously complex and doubtless involves many unknown factors. However, in the recorded studies of epidemics, certain fairly definite alterations in the distribution of the causal bacteria among the general population have been observed; the carrier rate both among healthy contacts and healthy noncontacts almost invariably rises. During epidemics of meningitis, for example, the carrier rate may rise to 80 per cent. among the contacts [1] in contrast to the average rate of about 2 per cent. in nonepidemic times and under average conditions. A similar phenomenon has been noted with the diphtheria bacillus,[2] the fixed type pneumococci [3] and streptococci.[4]

It seems of great importance, then, in the intelligent study of the spread of respiratory infections, to know as definitely as possible the "average," "normal" or "mean" distribution of the causal bacteria in nonepidemic times, in order that a departure from such a distribution may be accurately correlated with the occurrence of cases of disease. Such studies may yield criteria which will be helpful in differentiating sporadic from epidemic disease, a distinction which, as will be shown later, cannot always be made on a basis of the number of cases alone.

In the present instance it was our plan to obtain control material which would later be of help in explaining the mode of spread of acute

* From the biologic division of the medical clinic, the Johns Hopkins University and Hospital.

1. Glover: J. Hygiene **17**:350, 1918.
2. Graham-Smith: Bacteriology of Diphtheria, Cambridge, 1908, 1917.
3. Sydenstricker, V. P., and Sutton, A. C.: Bull. Johns Hopkins Hosp. **28**:312, 1917.
4. Blake, F. G.: Am. Otol., Rhinol., Laryngol. **28**:361, 1919.

tonsillitis in a community where this disease is prevalent each winter, and also to collect data on the "normal" state of parasitism of the hemolytic streptococcus in a group of people among whom streptococcus disease was not prevalent. It seemed important to find out not only the percentage of healthy persons who were carriers of hemolytic streptococcus, but also to study the type of parasitism from the standpoint of the number and distribution of the organisms in the upper air passages. With these facts recorded, one could later discover whether the cases of clinical streptococcus infection (tonsillitis) were preceded by any change in the number and distribution of the carriers, whether there was any alteration in the type of growth of streptococcus on the mucous membranes, whether such changes if present were a sequel of the disease outbreak, and whether the strains obtained from cases were identical with or different from those previously obtained from carriers. The fundamental importance of such data in relation to the definition of epidemic phenomena is obvious.

LITERATURE

The literature on the occurrence of the hemolytic streptococcus in the throats of normal people is large and too well known to require detailed review, but in spite of the volume of observations, little has been brought out which is helpful in interpreting epidemiologic phenomena. Reports concern themselves chiefly with the bare incidence of the organisms, the implication being that the percentage of positives depends largely on the technic of isolation employed. Arnold,[5] for example, in a recent summary of the literature, points out that various observers have recovered hemolytic streptococci in from 15 to 100 per cent. of "normal" people. Davis [6] found that if repeated pharyngeal cultures were taken from a group of normal students, sooner or later the beta hemolytic streptococcus was recovered. Davis and Pilot,[7] some years ago laid great stress on the presence of the hemolytic streptococcus in the tonsils and suggested that these organs were an important breeding place for strains which might later produce autogenous infection. This idea has been supported by others, and it is well known that the hemolytic streptococcus is less frequently found in the throats of those whose tonsils have been removed (Van Dyke,[8] Tongs [9]). The high incidence of hemolytic streptococcus in the men at certain camps during the war suggested that concentration of people might lead to rapid dissemina-

5. Arnold, L.: J. Lab. Clin. Med. **5**:3, 1920.
6. Davis, D. J.: J. Infec. Dis. **29**:524, 1921.
7. Pilot, I., and Davis, D. J.: J. Infect. Dis. **24**:386, 1919.
8. Van Dyke, H. B.: Hemolytic Streptococci in the Normal Throat After Tonsillectomy, J. A. M. A. **74**:448 (Feb. 14) 1920.
9. Tongs, M. S.: Hemolytic Streptococci in the Nose and Throat, J. A. M. A. **73**:1050 (Oct. 4) 1919.

tion (Fox and Hamburger,[10] Levy and Alexander[11]), but that this is not the only factor is indicated by the studies of Walker,[12] who found the incidence of hemolytic streptococcus in a military organization to be essentially the same (from 16 to 20 per cent.) in the recruits arriving, in those departing, and in the permanent personnel. It is of interest that streptococcus disease was absent in this unit during the time of the study.

It is clear, then, that many problems remain in regard to the significance and potential activity of the hemolytic streptococci found in the throats of healthy people. As such activity is undoubtedly profoundly altered at times when streptococcus disease is highly prevalent, it seemed, as suggested above, that the first step should be a careful study of the nature of streptococcus parasitism in a group of healthy people under average conditions. With this as base line, it would be much easier to interpret the more complex findings in epidemic conditions.

In another place,[13] emphasis was placed on the importance of serial, quantitative and topographical cultures in explaining the significance of bacteria found in the upper air passages. It was pointed out that the mere recovery of an organism in itself meant little, unless quantitative and topographical data were obtained as well. Thus, a single colony of *Staphylococcus aureus* isolated on one occasion by throat culture might be of no significance, whereas hundreds of colonies of the same germ recovered on repeated occasions from a localized region, such as the tonsil, would undoubtedly indicate a focal infection. Furthermore, an organism which grows diffusely over the mucous membranes of the mouth and throat may have a different significance from one which is confined to a local focus of diseased lymphadenoid tissue.

An attempt was therefore made in the present work to study the following points:

1. The incidence of beta hemolytic streptococcus in the throats of healthy people under average conditions at a time when streptococcus disease was not prevalent.

2. The exact location and the character of growth of hemolytic streptococcus in the throat under normal conditions to determine whether such growth is confined to a local focus (tonsil) or whether free growth on the mucous membranes take place.

3. The effect of introduction of convalescent carriers into a group on the distribution of hemolytic streptococcus.

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10. Fox, H., and Hamburger, W. W.: The Streptococcus Epidemic at Camp Zachary Taylor, Ky., J. A. M. A. **70**:1758 (June 8) 1918.

11. Levy, R. L., and Alexander, H. L.: The Predisposition of Streptococcus Carriers to the Complications of Measles, J. A. M. A. **70**:1827 (June 15) 1918.

12. Walker, J. E.: J. Infect. Dis. **27**:618, 1920.

13. Bloomfield, A. L.: The Serial Quarantitative Method of Culture in the Study of Respiratory Disease, J. A. M. A. **77**:187 (June 16) 1921.

4. Studies to determine the degree of dissemination of hemolytic streptococcus from carriers to contacts in nonepidemic times.

5. Relation of carrier state to history of previous streptococcus infection (tonsillitis).

MATERIAL AND METHODS

A group of about 200 women, students in the Johns Hopkins Hospital Nurses Training School, furnished material for the present study. Through the interested and intelligent cooperation of the supervisors of nurses, it was possible to keep the entire group under close observation, to obtain detailed information as to the exact location of their quarters in various dormitories, to obtain lists of room-mates, assignments to duty, etc., which were essential if useful contact studies were to be made. Furthermore, all cases of sickness, even mild colds, sore throats, or respiratory infections were reported daily to the resident physician of the hospital so that accurate data on the incidence of these conditions among the members of the group were available.

The bacteriologic survey for hemolytic streptococcus was made in the following way: A certain number of nurses reported to the laboratory daily for the taking of cultures. At that time a brief history and examination were recorded which included these points: the name, age, room number (dormitory), name of room-mate, date of entry to training school, history of colds or upper respiratory infections, history of tonsillitis, tonsillectomy (date), history of scarlet fever or other possible streptococcus infection, appearance of pharynx and tonsils with reference to size, crypts, scarring, adhesions, exudate, etc.

Three cultures were taken from each subject.

The first culture was taken from the pharynx. Taking care to avoid the tonsils and palate a straight cotton swab was vigorously rubbed over the posterior pharyngeal wall, covering the entire accessible area. The second culture was taken from the right tonsil. A 10 cm. piece of soft glass tubing 5 by 8 mm. in diameter was drawn out at one end to a capillary point about 1 to 1.5 mm. in diameter, and bent at an angle of 20 to 30 degrees. The wide end was stoppered with cotton, the pipet wrapped in paper and sterilized by dry heat. Before use, a piece of rubber tubing about 15 cm. long was attached to the wide end over the cotton plug. With the tongue well depressed, the capillary tube was inserted deeply into one or more tonsil crypts, and material for culture was aspirated by suction on the rubber tube. With a little practice, this procedure became simple. One usually obtained from the depths of the tonsil a drop or two of thick white or gray granular or pasty material. It was also possible with the pipet to break adhesions over crypts and to approach the interior of tonsils which appeared superficially intact. We should like to emphasize again that this procedure is a simple and satisfactory one for studying the tonsillar flora. It caused the subjects less discomfort than swabbing the throat, and there were no accidents or untoward effects from the manipulation. A third culture was taken from the left tonsil. The same method was used as in taking the culture from the right tonsil.

In subjects whose tonsils had been removed, a swab was taken from the pharynx and a second combined swab from both tonsil fossae.

The swabs from the pharynx and the material aspirated from the tonsils were immediately placed in tubes of meat infusion broth, and a series of dilutions were made in this medium. Small amounts of the diluted broth containing the bacteria were added to 10 c.c. portions of 5 per cent human blood meat infusion agar (p_H 7.4) which were shaken and poured into 15 cm. Petri plates. The plates were incubated at 37 C., and studied after twenty-four hours. The most difficult and essential point in the technic is to obtain an

abundance of colonies which are both well distributed and discrete so as to allow accurate counting and easy fishing. By using several dilutions it was possible in every case to obtain satisfactory plates.

Study of the Plates.—Attention was confined practically to the beta type of hemolytic streptococcus. It seems hardly necessary to refer to the original definition of Smith and Brown [14] and to the later descriptions of Brown,[15] but suffice it to say that consideration was given only to organisms which produced a total and usually relatively wide (1 to 2 mm.) zone of hemolysis about the colony, without any production of greenish discoloration. In the vast majority of cases there was no serious difficulty in picking out the real beta type colonies. In the occasional instance in which one seemed to be dealing with a borderline type—a colony about which the hemolytic zone was not absolutely complete, or one which together with hemolysis showed slight greenish discoloration—the difficulty was invariably cleared up on subculture when all such doubtful organisms were found definitely to be alpha or alpha prime and not beta types.

In each set of plates in which beta hemolytic streptococci were present, a careful note was made of the total number and of their relation to the other colonies. Special attention was given to the apparent identity of the hemolytic colonies when many were present, and a number of them (usually six) were fished to blood-agar slants, and preserved for further study. Later, practically all the strains were replated to insure purity, and were studied microscopically.

It may be stated at this point that no beta hemolytic strain has become essentially altered in its characteristics by subculture and storage—in no instance has any of them either lost their hemolytic activity or become green producers even after several months of artificial growth.

A word should be said about the terminology used in the following tables to express the number of colonies of beta hemolytic streptococcus recovered. No plate was considered satisfactory unless there was a heavy seeding of bacteria. When a note is made of "a few," "20," or any other small number of colonies of beta hemolytic streptococcus, these represent only a minute fraction of the total bacterial growth on the plate. On the other hand, when the designation "1/10" of the plate, "50 per cent." of the plate, or "pure culture" of beta hemolytic streptococcus is noted, it means not only a certain percentage of the total growth, but an absolutely large number of hemolytic streptococcus colonies as well. Furthermore, the results as expressed represent only

14. Smith, T., and Brown, J. H.: J. M. Res. **31**:455, 1915.
15. Brown, J. H.: Monograph 9, Rockefeller Institute, 1919.

in a relative way the real distribution of the bacteria in the throat. It is obviously impossible to make the procedure of culture absolutely uniform in every case, and the error is doubtless on the side of missing occasional streptococcus carriers, although we feel sure that this will apply only to the rare transient carrier with an extremely slight degree of infestation.

TABLE 1.—*Results of Cultures for Hemolytic Streptococcus in 108 Healthy Women Whose Tonsils Had Previously Been Removed*

Case Number	Date of Culture	Number of Colonies of Beta Hemolyticus Streptococcus Recovered from Pharynx	Number of Colonies of Beta Hemolyticus Streptococcus Recovered from Tonsil Fossae	Remarks
6	9/ 7/22	0	0	
7	9/ 7/22	0	0	
16	9/ 8/22	0	0	
17	9/ 9/22	0	0	
18	9/10/22	0	0	
22	9/11/22	0	0	
24	9/14/22	0	0	
28	9/14/22	0	0	
36	9/14/22	0	0	
37	9/14/22	Few†	0	Tonsillectomy 3 years ago
39	9/15/22	0	0	
41	9/15/22	0	0	
43	9/15/22	Few	Few	Tonsillectomy 11 years ago
44	9/15/22	0	0	
48	9/15/22	0	0	
51	9/18/22	Few	Few	Tonsillectomy 5 years ago
52	9/18/22	0	0	
56	9/18/22	0	0	
60	9/19/22	0	0	
62	9/19/22	0	0	
75	9/22/22	0	0	
77	9/22/22	0	0	
78	9/22/22	0	0	
79	9/22/22	0	0	
80	9/22/22	0	0	
82	9/25/22	0	0	
85	9/25/22	0	0	
90	9/25/22	0	0	
92	9/25/22	0	2	Tonsillectomy 1 year ago
94	9/25/22	0	0	
95	9/25/22	0	0	
96	9/25/22	0	0	
99	9/26/22	0	0	
101	9/26/22	0	0	
102	9/26/22	0	3	
104	9/27/22	0	0	
106	9/27/22	0	0	
107	9/27/22	0	0	
108	9/30/22	0	0	
111	9/30/22	0	0	
114	9/30/22	0	0	
115	9/30/22	0	0	

* Total cases, 42; negative, 38 or 90.5 per cent.; positive, 4 or 9.5 per cent.
† Few indicates less than six colonies, and less than 1 per cent. of total colonies on plate.

In every culture in which many colonies of hemolytic streptococcus were present, all seemed to be identical. This impression was almost invariably supported, as will be pointed out in a later paper, when several colonies were fished and studied. It is quite possible, however, that two or more strains of hemolytic streptococcus may occasionally be present in the same throat, but such a state of affairs would bear no significant relation to our conclusions.

RESULTS

Incidence and Distribution of Beta Hemolytic Streptococcus in the Throats of Healthy People at a Time When Streptococcus Disease Was not Prevalent.—During the month of September, 1922, cultures were made from 108 healthy students. There had been one case of acute tonsillitis in the training school during the last week of August, but no cases during June or July, and there were no cases during September. The experiment, therefore, seemed absolutely valid from the standpoint of representing "average" or "normal" conditions in a community at a time when streptococcus infection (tonsillitis) was not present.

The results of the cultures are given in Tables 1 and 2. Thirty-one, or 28.7 per cent., of the total group of 108 yielded beta hemolytic streptococcus. A study of the tables, however, immediately discloses a remarkable difference between those whose tonsils have been removed and those in whom the tonsils are intact. Of the former group of forty-two people, only four, or 9.5 per cent., harbored the organism and only in small numbers. Occurrence of a few scattered colonies of a foreign organism on the mucous membrane of the throat indicates almost always, as we have shown elsewhere,[16] an insignificant transient infestation. It seems perfectly clear that these tonsillectomized persons were not the subjects of a chronic carrier state and that the organisms had been introduced by chance, perhaps from another person and were of no more significance than an inanimate foreign particle. On the other hand, the group of persons whose tonsils were intact exhibited entirely different conditions. A much larger percentage of the group (41 per cent.) were carriers, and the number and distribution of the bacteria were different. A study of Table 2 shows that in this group the hemolytic streptococcus carrier state was essentially one of focal tonsillar infection. The streptococci were recovered with frequency and often in huge numbers from the depths of the tonsils when not a single colony was obtained from the pharynx, and in no case were they obtained from the pharynx unless the tonsil culture showed them as well, and usually in much greater numbers. It is certain, as we have shown elsewhere,[17] that in most of these people the streptococci recovered from the pharynx represented merely an overflow or spread by direct contact from the breeding place in the tonsil, and that they were not actually colonizing and growing on the free mucous membrane.

Summary: These cultures allow an exact definition of the nature of beta hemolytic streptococcus parasitism under average conditions in healthy people when streptococcus disease is not present. Such parasitism is strictly a focal one in areas of infected lymphadenoid tissue.

16. Bloomfield, A. L.: Bull. Johns Hopkins Hosp. **32**:290 (Sept.) 1921.
17. Bloomfield, A. L.: A. J. M. Sc. **164**:854, 1922.

TABLE 2.—*Results of Cultures for Hemolytic Streptococcus in 108 Healthy Women Whose Tonsils Had Not Been Removed* *

Case No.	Date	Number of Colonies of Beta Hemolyticus Streptococcus from			Appearance of Tonsils	History of Tonsillitis
		Pharynx	Right Tonsil	Left Tonsil		
2	9/ 7/22	0	0	0	Medium, clean; many crypts	Negative
3	9/ 7/22	0	0	0	Large, clean; many crypts	Negative
4	9/ 7/22	0	0	0	Small stumps; partial tonsillectomy	Last attack 8 yrs. ago
5	9/ 7/22	0	0	0	Small, clean; no visible crypts	Last attack 8 mos. ago
8	9/ 7/22	0	0	0	Huge, scarred adhesions; many large crypts	Last attack 1 yr. ago
9	9/ 7/22	0	0	0	Small, clean; many crypts	Negative
10	9/ 7/22	0	No culture	0	Small, clean, deep set; no crypts seen	Negative
11	9/ 7/22	0	Many 50% of plate	0	Large, globular, clean; concealed crypts	Last attack within last 9 mos.
12	9/ 8/22	0	Many 10% of plate	0	Large, scarred adhesions; many sealed crypts	Last attack 6 mos. ago
13	9/ 8/22	0	0	0	Small, clean, deep set; few sealed crypts	Last attack 10 yrs. ago
14	9/ 8/22	0	0	0	Very large globular tonsils	No attack for several years
19	9/11/22	0	0	0	Very small, clean; many crypts	One attack 2 yrs. ago
20	9/11/22	0	0	0	Very small, clean; few sealed crypts	Negative
21	9/11/22	0	No culture	0	Small stumps with crypts; partial tonsillectomy	Last attack 2 yrs. ago
25	9/12/22	0	0	0	Small, clean, deep set	Negative
26	9/12/22	0	0	0	Large, clean, scarred	Last attack 1½ yrs. ago
27	9/15/22	0	Many 10% of plate	Many 10% of plate	Large, clean, scarred	Last attack 1½ yrs. ago
28	9/15/22	0	0	0	Huge, globular; many crypts	Last attack 6 yrs. ago
29	9/15/22	1% of plate	50% of plate	33% of plate	Very small, deep set, clean	No attack for yrs.
30	9/15/22	20 colonies	2 colonies	0	Large, scarred; many crypts	Last attack 10 mos. ago
33	10/ 7/22	0	0	0	Medium, many crypts	Last attack 2 mos. ago
38	9/15/22	0	0	0	Small, deep set; many crypts	Last attack 9 yrs. ago
40	9/15/22	20% of plate	Many pure cult.	0	Huge, congested; many sealed crypts	Last attack 11 mos. ago
42	9/15/22	1% of plate many	1% of plate	1% of plate many	Large, ragged, scarred	Last attack 1 yr. ago
45	9/15/22	20% of plate	80% of plate	0	Very small, clean	Last attack 4 yrs. ago
46	9/16/22	0	0	0	Very large, clean, scarred	Last attack 4 mos. ago
47	9/18/22	0	0	0	Medium, deep set, clean, scarred	Negative
49	9/18/22	4 colonies	Almost pure cult.	0	Large, globular, clean	Negative; scarlet fever 1 yr. ago
50	9/18/22	0	1% of plate	1% of plate	Very large, clean; many crypts	Last attack 8 mos. ago
53	9/18/22	0	0	0	Very large, globular scarred, clean	Last attack 4 yrs. ago
54	9/18/22	0	No culture	0	Small, deep set, clean	Negative
55	9/18/22	1 colony	Almost pure cult.	Many over 10%	Deep set, clean.....	Last attack 6 mos. ago
57	9/18/22	0	No culture	Many over 10%	Huge, scarred, ragged especially left	No attack for 13 years
58	9/20/22	Few	20 colonies	3 colonies	Huge, clean; many crypts	Last attack 5 mos. ago
59	9/20/22	0	No culture	0	Very small, deep set	Last attack 5 yrs. ago

* Total cases, 66; negative 39, or 59 per cent.; positive 27, or 41 per cent.

TABLE 2.—*(Continued)*

Case No.	Date	Number of Colonies of Beta Hemolyticus Streptococcus from			Appearance of Tonsils	History of Tonsillitis
		Pharynx	Right Tonsil	Left Tonsil		
61	9/20/22	0	50% of plate	50% of plate	Large, deep set, clean	Last attack 6 yrs. ago
62	9/20/22	0	0 surface culture	0 surface culture	Tonsils not definitely visible	Last attack 5 yrs. ago
64	9/20/22	0	No culture	1 colony	Very small, deep set; few large crypts	Two attacks in past year
65	9/20/22	Many colonies	Many colonies, surface cult.	Many colonies, surface cult.	No tonsil visible.....	Last attack 6 mos. ago
66	9/20/22	0	No culture	0	Medium, clean.....	Negative
67	9/20/22	0	0	0	Very small, deep set	Negative
68	9/20/22	0	0	0	Very small, clean, deep set	Negative
70	9/22/22	0	0 surface culture	0 surface culture	Partial tonsillectomy; large stumps	Last attack 6 yrs. ago
71	9/22/22	0	0	0	Small, clean.....	Negative
72	9/22/22	0	0 surface culture	0 surface culture	Small, clean.....	None recently
73	9/22/22	Few	No culture	No culture	Small, deep set.....	None recently
76	9/22/22	Few	50% of plate	50% of plate	Partial tonsillectomy; small stumps	Last attack 9 mos. ago
81	9/25/22	No culture	Few	Few	Large, deep set, clean	None recently
83	9/25/22	0	0	0	Large, scarred, clean; many crypts	Last attack 7 mos. ago
84	9/25/22	0	0	50% of plate	Large, clean.....	Negative
86	9/25/22	0	0	Few; less than 1%	Small, deep set, ragged, clean	Last attack 7 yrs. ago
87	9/22/22	0	0 surface	0 surface	Small, clean, deep set	Last attack 15 yrs. ago
88	9/25/22	0	Almost pure cult.	0	Large, clean.....	Negative
89	9/25/22	0	0	0	.....	Negative
91	9/25/22	Few	Few	Few	Small, clean tonsils....	Last attack 1913
93	9/25/22	0	0	0	Huge, globular, clean; many crypts	None recently
97	9/26/22	0	0	0	Clean, large; many crypts	Last attack 1 yr. ago
98	9/26/22	0	0	0	Large, clean, deep set	Last attack 5 yrs. ago
100	9/26/22	0	0	0	Large, clean.....	Last attack 1 yr. ago
103	9/27/22	0	Many	Almost pure cult.	Large, ragged, deep set	Last attack 1 yr. ago
105	9/27/22	0	0	0	Small, deep set, clean	None recently
109	9/30/22	0	0	0	Small, clean.....	Negative
110	9/30/22	0	0	0	Small, ragged.....	Negative
112	9/30/22	Few	0	Very few	Small, deep set.....	Last attack 5 yrs. ago
113	9/30/22	0	Few	0	Large, clean.....	Last attack 1 yr. ago
116	9/30/22	0	0	0	Medium, deep set.....	Last attack 3 yrs. ago

such as the tonsil, and there is no evidence that the bacteria are actually growing and multiplying on the free surfaces of the mucous membrane, although a few may be spread by direct contact from the tonsil over the pharyngeal wall. The occasional colony recovered from tonsillectomized persons clearly indicates, as a rule, a transient "pick-up" and not a true chronic carrier state.

Effect of Occurrence of cases of Tonsillitis and Introduction of Convalescent Carriers into the Group on the Type of Streptococcus Parasitism.—During the early part of October, 1922, acute tonsillitis

began to appear in the group, and during this month there were nine cases. All these patients yielded innumerable colonies of hemolytic streptococci from the throat and tonsils. After an average hospitalization of one week, they reentered the group, although culture showed that they still harbored tremendous numbers of hemolytic streptococcus. To determine whether the occurrence of tonsillitis was associated with any change in the normal type of parasitism defined above, as well as to study the effect of introducing heavily infected convalescent carriers into the group, a set of cultures was made during October, 1922, on a second series of sixty-seven healthy subjects similar in every way to the first, both as to methods and material. The results are analyzed in Tables 3 and 4, and are summarized in Table 5.

TABLE 3.—*Results of Cultures for Hemolytic Streptococcus in Healthy Women Whose Tonsils Had Previously Been Removed* *

Case Number	Date of Culture	Number of Colonies of Beta Hemolyticus Streptococcus Recovered from		Remarks
		Pharynx	Tonsils	
121	10/ 9/22	0	0	
122	10/ 9/22	0	0	
123	10/ 9/22	0	0	
124	10/ 9/22	0	0	
133	10/10/22	0	0	
134	10/10/22	0	0	
136	10/10/22	0	0	
139	10/10/22	1	0	Tonsillectomy 3 weeks ago
140	10/10/22	0	0	
142	10/10/22	0	0	
145	10/11/22	0	0	
147	10/11/22	0	0	
152	10/13/22	0	0	
157	10/16/22	0	0	
158	10/16/22	0	0	
159	10/16/22	0	0	
160	10/16/22	0	0	
168	10/16/22	0	0	
169	10/18/22	0	0	
171	10/18/22	Practically pure culture	1	Tonsillectomy 2 months ago
174	10/18/22	0	0	
178	10/18/22	0	0	
182	10/20/22	0	0	
187	10/20/22	0	0	
191	10/20/22	0	0	

* Total cases, 25; positive 2, or 8 per cent.; negative 23, or 92 per cent.

A study of these tables shows a striking agreement between the two sets of cultures both as to the total incidence of beta hemolytic streptococcus and as to the quantitative topographical distribution of the bacteria. As a matter of fact, the percentage of positives was a little lower after streptococcus disease became prevalent. Case 171 was the single exception, showing a practically pure culture from the pharynx of a tonsillectomized person; but it should be noted that the tonsils were removed only two months previous to culture, and that a stump was left on one side.

TABLE 4.—*Results of Cultures for Hemolytic Streptococcus in Healthy Women Whose Tonsils Had Not Been Removed* *

Case No.	Date	Number of Colonies of Beta Hemolytic Streptococcus from			Appearance of Tonsils	History of Tonsillitis
		Pharynx	Right Tonsil	Left Tonsil		
125	10/ 9/22	0	0 surface culture	0 surface culture	Partial tonsillectomy 4 years before; stumps ragged	No attack for 4 years
126	10/ 9/22	0	0	0	Huge, ragged	Last attack 1 year ago
127	10/ 9/22	0	0	0	Large, clean	Negative
128	10/ 9/22	0	0	0	Small, clean, deep set	Negative
131	10/10/22	0	0	0	Medium, ragged	Last attack 1 year ago
132	10/10/22	Few	Almost pure cult.	Almost pure cult.	Huge, clean; large crypts	Last attack 3 yrs. ago
135	10/10/22	Few	Few	0	Large, ragged, scarred	Negative
137	10/10/22	0	Few	Few	Very large, ragged	Last attack 1 year ago
138	10/10/22	0	0	0	Small, clean	Negative
141	10/10/22	0	0 surface	0 surface	No definite tonsils visible	None recently
143	10/11/22	0	0	0	Large, clean	Negative
144	10/11/22	0	0	0	Right tonsil not seen; left tonsil small, clean	Negative
146	10/11/22	0	0	0	Huge, clean; many crypts	Negative
148	10/11/22	0	0	0	Large, clean	Negative
149	10/11/22	0	Many 10% of plate	Many 10% of plate	Small, deep, clean	Negative
150	10/11/22	0	0	0	Small, clean	Last attack 9 mos. ago
151	10/13/22	0	0 surface	0 surface	Small, clean	Last attack 15 months ago
153	10/13/22	0	0	Few	Moderate, adherent, clean	Last attack 7 mos. ago
154	10/13/22	1	Very many over 10%	Many over 10%	Small, clean	None recently
155	10/13/22	0	0	0	Medium, adherent, clean	Last attack 4 yrs. ago
156	10/13/22	0	0	0	Medium, adherent, clean	Last attack 17 yrs. ago
161	10/16/22	0	0	0	Medium, clean	Last attack 3 mos. ago
162	10/16/22	0	0	0	Small, clean	Last attack 4 yrs. ago
163	10/16/22	0	0	0	Medium, clean	Negative
164	10/16/22	0	No cultures	0	Medium, clean	Negative
165	10/16/22	1 colony	Few	0	Large, clean	Negative
167	10/16/22	0	0	0	Large, ragged	Negative
170	10/18/22	0	0	0	Large, clean	Last attack 2 yrs. ago
172	10/18/22	0	0	0	Medium, clean	Negative
173	10/18/22	Few	0	Few	Medium, clean	Last attack 2 yrs. ago
175	10/18/22	0	0	0	Medium, clean	Last attack 20 months ago
176	10/18/22	0	0	50% of plate	Small, clean	Last attack 8 mos. ago
179	10/18/22	0	0 surface	0 surface	Medium, ragged	Negative
183	10/20/22	Few	Few	Few	Small, clean; crypts	Negative
184	10/20/22	0	0	0	Large, ragged	Negative
185	10/20/22	0	0	0	Very small, barely visible	Negative
186	10/20/22	0	1 colony, surface swab both tonsils		Partial tonsillectomy; ragged stumps; crypts	Negative
188	10/20/22	0	0	0	Very large, clean	Negative
189	10/20/22	1 colony	Almost pure cult.	0	Very large, clean	Negative
190	10/20/22	0	Pure culture	Pure culture	Large, ragged, clean	Negative
192	10/20/22	0	Many	Many	Large, clean	Negative
198	10/20/22	0	0	0	Very large, ragged, clean	Last attack 8 yrs. ago

* Total cases, 42; positive 14, or 33 per cent.; negative 28, or 67 per cent.

Summary: The occurrence of acute tonsillitis was unassociated with any general change in streptococcus parasitism in the group, nor did the reintroduction of heavily infected convalescent carriers produce any alteration. This point will be developed in a later paper in connection with the epidemiology of tonsillitis.

Dissemination of Hemolytic Streptococcus from Carriers to Contacts During a Nonepidemic Time.—The preceding observations seemed to indicate that under ordinary conditions, when streptococcus disease was not epidemic, there was no tendency to the development of secondary carriers by contact between the uninfected and infected healthy members of the group. To settle this point, an analysis was made of fifty-one pairs of room-mates. These pairs had been rooming together for at least several weeks before the cultures were made, and there had been every opportunity for close contact. The results of the cultures are shown in Table 6. On the law of chance alone, one would have expected at least eight pairs to be positive instead of four, so that there can be no question but that contact between healthy people played no part in the establishment of the carrier state in this group.

TABLE 5.—*Comparison of Cultures Made Before and After Streptococcus Disease (Tonsillitis) Was Prevalent*

Series	Tonsillectomized			Nontonsillectomized		
	Total	Percentage Positive	Percentage Negative	Total	Percentage Positive	Percentage Negative
I. September, 1922, before streptococcus disease appeared...	42	9.5	90.5	66	41.0	59.0
II. October, 1922, after streptococcus disease appeared.....	25	8.0	92.0	42	33.0	67.0
Combined total.....	67	9.0	91.0	108	37.0	63.0

Relation of Carrier State to Previous Streptococcus Infection (Tonsillitis).—It was clear, then, that some other explanation besides contact must be sought to explain the occurrence of streptococcus carriers. As the organisms were essentially confined to the tonsil, it seemed possible that all the carriers dated from an original acute streptococcus infection of the tonsil (tonsillitis). From 130 members of our group, it was possible to obtain accurate statements as to preceding acute attacks. These histories correlated with the bacteriologic findings are analyzed in Table 7. The figures suggest strongly that the foregoing assumption is correct and that the chronic carrier state represents a residue of an acute tonsillitis. The 20 per cent. of carriers in the group with negative history may be partly explained by infection dating from a mild attack of tonsillitis which did not impress the patient. We have had the opportunity to observe several such cases which were

quite definite but which were unassociated with fever or much sore throat. They will be discussed later in connection with the clinical features of tonsillitis.

TABLE 6.—*Occurrence of Hemolytic Streptococcus in Room-Mates*

Case Number	Date of Culture	Hemolytic Streptococcus	Case Number	Date of Culture	Hemolytic Streptococcus	Case Number	Date of Culture	Hemolytic Streptococcus
193	10/20/22	Negative	153	10/13/22	Positive	115	9/30/22	Negative
190	10/20/22	Positive	106	9/27/22	Negative	6	9/ 7/22	Negative
191	10/20/22	Negative	151	10/13/22	Negative	112	9/29/22	Positive
165	10/16/22	Positive	58	9/20/22	Positive	88	9/22/22	Positive
189	10/20/22	Positive	148	10/11/22	Negative	111	9/29/22	Negative
160	10/16/22	Negative	46	9/16/22	Negative	48	9/18/22	Negative
188	10/20/22	Negative	147	10/11/22	Negative	100	9/29/22	Negative
173	10/20/22	Positive	126	10/ 9/22	Negative	66	9/20/22	Negative
187	10/20/22	Negative	146	10/11/22	Negative	108	9/29/22	Negative
97	9/26/22	Negative	49	9/18/22	Positive	64	9/20/22	Negative
186	10/20/22	Positive	145	10/11/22	Negative	98	9/26/22	Negative
175	10/18/22	Negative	108	9/26/22	Positive	67	9/20/22	Negative
184	10/20/22	Negative	144	10/11/22	Positive	93	9/22/22	Negative
65	9/20/22	Positive	80	9/25/22	Negative	94	9/22/22	Negative
183	10/20/22	Positive	141	10/10/22	Negative	84	9/24/22	Positive
170	10/18/22	Negative	128	10/ 9/22	Negative	4	9/ 7/22	Negative
171	10/18/22	Positive	139	10/10/22	Positive	74	9/21/22	Negative
179	10/18/22	Negative	116	9/29/22	Negative	28	9/12/22	Negative
163	10/16/22	Negative	136	10/10/22	Negative	73	9/21/22	Positive
176	10/18/22	Positive	102	9/26/22	Negative	2	9/24/22	Negative
192	10/20/22	Positive	135	10/10/22	Positive	71	9/21/22	Negative
174	10/18/22	Negative	38	9/15/22	Negative	40	9/15/22	Positive
80	9/22/22	Negative	133	10/10/22	Negative	68	9/19/22	Negative
172	10/18/22	Negative	42	9/15/22	Positive	50	9/18/22	Positive
168	10/18/22	Negative	132	10/10/22	Positive	63	9/20/22	Negative
164	10/16/22	Negative	37	9/15/22	Positive	60	9/20/22	Negative
72	9/22/22	Negative	131	10/10/22	Negative	61	9/20/22	Positive
162	10/16/22	Negative	36	9/18/22	Positive	57	9/18/22	Positive
161	10/16/22	Negative	127	10/ 9/22	Negative	54	9/18/22	Negative
156	10/13/22	Negative	121	10/ 9/22	Negative	53	9/18/22	Negative
138	10/10/22	Negative	125	10/ 9/22	Negative	50	9/18/22	Positive
155	10/13/22	Negative	47	9/16/22	Negative	36	9/15/22	Negative
110	9/29/22	Positive	123	10/ 9/22	Negative	33	10/ 7/22	Negative
154	10/13/22	Positive	41	9/15/22	Negative	15	9/ 9/22	Positive
14	9/ 8/22	Negative						

Total pairs of room-mates, 51; both positive, 4; both negative, 23; one positive, one negative, 24.

Relation of Streptococcus Carriage to Appearance of Tonsil.—Finally, it seemed of interest to correlate the presence of the hemolytic streptococcus with the clinical appearance of the tonsils. A sharp classification was impossible. However, we have divided the tonsils into three groups: Group 1, small, clean, without adhesions, scars or large crypts—tonsils of "innocent" and insignificant appearance; Group 3, large, scarred, or adherent tonsils usually with plugged crypts

—the type usually condemned by the laryngologist; and Group 2, tonsils intermediate in appearance between Groups 1 and 3. The results of culture in the three groups are summarized in Table 8.

TABLE 7.—*Relation of Streptococcus Carriage to History of Tonsillitis*

History of an Attack of Tonsillitis	Total Number of Cases	Percentage Positive for Beta Hemolytic Streptococcus
Within 6 months before culture	30	83.4
Six months to two years before culture	27	52.0
Over two years before culture	33	33.3
No history of tonsillitis	40	20.0

TABLE 8.—*Relation of Appearance of Tonsil to Positive Culture of Streptococcus Hemolyticus*

Group	Total Number of Cases	Number Positive	Percentage Positive
1	38	12	30.2
2	27	9	33.3
3	33	16	49.0

It appears that the obviously diseased tonsils yield hemolytic streptococcus more often than those of innocent appearance, although the latter are frequently infected with this organism.

SUMMARY AND DISCUSSION

Despite the great amount of clinical, biometric and bacteriologic study which is on record, no general laws have been deduced which are altogether satisfactory in explaining the spread of bacterial infection. It appears that the operation of different forms of infectious agents under various conditions may be so diverse that epidemic phenomena, while resembling each other in a broad way, may be quite dissimilar in their intimate details. In the case of the present problem—infection with *Streptococcus hemolyticus*—the useful mode of approach has seemed to be from the standpoint of the deviation from the "normal," "average," or "mean" type of parasitism of this organism, and the immediate object of this report is to define in as accurate terms as possible such a "norm." A detailed study has therefore been made of the quantitative topographical distribution of hemolytic streptococcus in the upper air passages of an average group of healthy persons and of the effect of certain possible disturbing factors on such a distribution.

The major conclusion is that the hemolytic streptococcus under average conditions is strictly adapted to a local growth in foci of lymphadenoid tissue in the upper air passages, especially the tonsil. In such foci these bacteria may persist for long periods of time and

in great numbers—we obtained no evidence of a free growth on the mucous membranes in general. It appears, furthermore, that such colonization is usually brought about by an acute, clinically manifest, infection of the lymphadenoid tissue, such as acute tonsillitis, or perhaps scarlet fever. Such an infection seems necessary, under average conditions, in order that the bacteria may gain a lasting foothold. Careful study of carriers and noncarriers who roomed together seemed to prove that mere contact, even if close and prolonged, is inadequate—under average conditions—to give rise to new carriers. Again, it was found that neither the incidence of healthy carriers nor the local lymphoid tissue type of parasitism was altered by introducing into the group tonsillitis convalescents harboring presumably actively vegetative organisms. The exact relationship of preexisting carriers to fresh cases of acute tonsillitis will be discussed in a subsequent paper.

Finally, further evidence of the essentially focal nature of hemolytic streptococcus parasitism under "normal" conditions is found in the fact that of those whose tonsils have been removed only an occasional person harbored the organism, and then in small numbers, indicating a transient infestation rather than a true growth adaptation.

Such then is the definition of the status of streptococcus hemolyticus parasitism under normal conditions when streptococcus disease is either absent or sporadic in type. But observations on record in the literature show that when streptococcus disease is highly epidemic, a type of parasitism which is quite different may exist. Under such conditions, for example in the army camps, it was found [4] that practically every man both sick and well was a streptococcus carrier, and also that the organisms apparently were growing freely and generally on the mucous membrane of the throat, and were by no means confined to local lymphadenoid foci. A radical change in the type of parasitism had occurred. The nature and significance of this change will be discussed at another time. At present the fact is mentioned to stress by contrast the "normal" or "average" stable type of parasitism described above, which apparently must be fundamentally upset before epidemic streptococcus disease can occur.

STUDIES ON LIVER FUNCTION

ROSE BENGAL ELIMINATION FROM THE BLOOD AS INFLUENCED BY LIVER INJURY *

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In recent years, the interest of a number of investigators has centered on the question of liver function. It is hardly necessary at the present time to discuss these tests in detail as a review by Delprat and Whipple [1] covers much of this ground. Whipple and Pelkan [2] have recently reported experiments which indicate that phenol conjugation is a function of the liver which gives information of value in a study of the physiology of the liver. Phenol ingestion is too toxic for clinical use. Many papers [3] dealing with the injection of phenoltetrachlorphthalein have appeared during the past few years. This dye is eliminated promptly from the blood by the liver and appears in the bile and intestine. Various methods of recovery of the dye from the feces or duodenum have been used, but this test is inaccurate when there are abnormalities of the biliary passages and therefore has obvious clinical limitations. Since the completion of these experiments, two papers by Rosenthal [4] have appeared dealing with a utilization of tetrachlorphthalein in the blood stream. His experiments were almost identical with the experiments given below in which a new dye, rose bengal is used. Our experiments in many respects confirm the observations of Rosenthal.

An ideal dye for this type of work must fulfil the following requirements: (*a*) It must be nontoxic; (*b*) it must be a crystalloid (we know that the fate of colloid dyes in the organism is entirely different from that of the diffusible dyes); (*c*) it must be eliminated from the organism by means of the activity of liver parenchyma cells, and (*d*) it must remain in the circulation for a sufficient length of time to allow determinations of the dye concentration in the blood plasma to be made. All these requirements are fulfilled in the substance rose bengal

* From the George Williams Hooper Foundation for Medical Research, University of California Medical School, San Francisco.

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4. Rosenthal, S. M.: J. Pharm. & Exper. Therap. **19**:385, 1922; Proc. Soc. Exper. Biol. & Med. **20**:86, 1922.

(tetraiodotetrabrom fluorescene). This substance is nontoxic in large doses (3 gm. were tolerated by a 30 pound (13.6 kg.) dog while 5 gm. were fatal in five hours); it is a crystalloid, and it remains in the normal circulation.

In 1918, an opportunity was afforded me for a study of a large series of the fluorescene and triphenylmethane dyes for the purpose of finding a "liver function dye." This work was carried out in the anatomical laboratory of the University of California under the guidance of Dr. H. M. Evans. The first experiments were carried out on rats, and those dyes which (after injection into the circulation of the animal) appeared only in the stools were subsequently injected into dogs with bile fistula. Several of the dyes which in the rat were eliminated only in the stools were excreted in the urine of the dog. However, one dye, rose bengal, was found to be eliminated entirely in the bile of both the rat and dog, even when injected in large doses. At no time did it appear in the urine.

Attempts were made to carry out determinations to ascertain the percentage of recovery in the bile. On account of the interference of the bile pigments, colorimetric estimations of small amounts of the rose bengal were impossible with any degree of accuracy, and chemical methods by which the bile pigments were precipitated were unsatisfactory, since part of the dye was carried down in the precipitate.

If the liver is the only organ concerned with the elimination of the dye, as it appears to be, then the rate of disappearance of the dye from the blood stream after injection should be definitely influenced by the liver activity or by the extent of the liver injury. It is to be expected that the dye will remain longer in the circulation of the animal whose liver is injured than in the blood stream of the normal animal.

METHOD

The method which was used in the following experiments is almost similar to the "dye method" of determining plasma volume.[5] It may be briefly outlined as follows:

(1) A measured amount of a 1 per cent. solution of the dye is delivered into an evaporating dish and drawn into a 10 c.c. record syringe. The evaporating dish is rinsed with a few drops of saline, which is also drawn into the syringe, and the rinsing is repeated until the evaporating dish shows no traces of the dye. This syringe is then laid aside.

(2) About 10 c.c. of blood are drawn from the jugular vein of the dog into a clean syringe, and in turn are delivered into a graduated

5. Hooper, C. W.; Smith, H. P.; Belt, A. E., and Whipple, G. H.: Am. J. Physiol. **51**:205, 1920.

centrifuge tube containing 2 c.c. of 2 per cent. potassium oxalate solution. This is a control sample.

(3) With the needle in situ, the solution of the dye in the syringe which was laid aside is injected into the circulation and the time is noted. The plunger is drawn back and forth to rinse out the barrel and the needle, this process being continued until the next step. The last manipulation reduces the amount of dye that may possibly remain in the needle to an extremely small quantity, which may then be neglected.

(4) One minute from the time of the beginning of the injection a sample of from 8 to 10 c.c. of blood is withdrawn into a clean syringe, and is delivered into a centrifuge tube identical with the one previously used.

(5) At two, four, eight and sixteen minutes from the time when the injection began, samples of blood are withdrawn from the jugular vein, and are delivered into centrifuge tubes containing a solution of potassium oxalate. It is usually advisable to withdraw the needle after taking the four minute sample and to make a fresh puncture for both the eight and the sixteen minute samples, to avoid the possibility of clot formation.

(6) The six centrifuge tubes containing the samples are then centrifugalized for thirty minutes at 3,000 revolutions per minute.

(7) After noting the volume of blood in the graduated centrifuge tubes, 3 c.c. of plasma from each of the samples are delivered into a clean test tube, and are diluted with 6 c.c. of normal saline, care being taken to wash the pipet with saline before it is used for the next specimen. Samples of each of these diluted plasma solutions are then placed in a Hellige colorimeter and read against a standard prepared as follows: Five c.c. of normal blood plasma (from the control tube) are diluted with 5 c.c. of saline, and to this are added 5 c.c. of a 0.0075 per cent. solution of the rose bengal (made by diluting 0.75 c.c. of a 1 per cent. solution of the dye to 100 c.c. distilled water).

(8) Allowance must be made for the volume of the oxalate solution which is added to the blood in the hematocrit tube. If 10 c.c. of blood are added to 2 c.c. of oxalate, it is evident that the colorimetric reading must be multiplied by 12/10 to allow for the dilution of the blood. These corrected readings are given in the tables.

EXPERIMENTS SHOWING RATE OF ELIMINATION OF DYE FROM BLOOD STREAM AND THE INFLUENCE OF LIVER INJURY ON RATE OF ELIMINATION

Experiments were carried out on dogs whose livers were injured by chloroform to determine the rate of disappearance of rose bengal after injection into the blood stream. In each instance the rate of dis-

appearance of the dye from the blood stream was determined prior to the injury of the liver of the particular animal which was used for the experiment. The colorimeter readings represent the percentage concentration of the dye in the plasma as compared with the standard (0.0075 per cent.). Since the plasma volumes from day to day under these experimental conditions are not constant, it is impossible to compare these readings directly. The effect of varying plasma volume may be eliminated by computing the ratios of the colorimetric readings at the two, four, eight and sixteen minute interval. If these ratios are plotted against the corresponding time intervals, a 'rate of dye elimination curve' will be obtained. This ratio decreases rapidly during the first intervals of time and less so at later time intervals.

Tables 1 to 4 show the effect of liver injury by chloroform anesthesia on the rate of elimination of the dye from the blood stream.

TABLE 1.—*Percentage Concentration of Rose Bengal in the Blood Plasma Before and After Liver Injury by Chloroform Anesthesia*

Dog 22-40 (Adult Black and White Hound)*

	Colorimetric Readings and Values for Bt at Intervals of									
	One Minute,	2 Minutes		4 Minutes		8 Minutes		16 Minutes		
Date, 1922	Percentage	Percentage	B	Percentage	B	Percentage	B	Percentage	B	Weight, Pounds	Plasma Volume, C.c.
3/ 7	90	88	0.89	69	0.70	38	0.39	22	0.22	24.5	405
3/ 8	98	85	0.87	64	0.64	45	0.46	23	0.23	23.5	408
3/ 8	Chloroform anesthesia 50 minutes										
3/ 9	104	100	0.97	89	0.86	83	0.80	70	0.67	22.8	286
3/11	106	96	0.91	87	0.81	83	0.78	52	0.48	21.8	377
3/14	94	80	0.85	72	0.76	48	0.50	36	0.38	21.8	425
3/16	96	86	0.90	75	0.78	57	0.60	40	0.42	21.8	430

* The dog was isolated on March 5 and food was withheld until the experiment was completed. On March 9, the day following the anesthesia, the plasma was brightly colored with bile pigments, but less so on March 11 and only slightly so on March 14. The dog did not vomit or show signs of severe toxicity. He drank a copious amount of water.

† In this and other tables, B represents the ratio of the percentages of dye at any particular time to the percentage after the first minute interval. The dose of rose bengal equals 30 mg. for each injection.

In none of these cases did the injury prove fatal to the animal. It may be assumed that the animals were normal prior to the period of anesthesia. Nearly identical curves were obtained during the normal period of the same dog, and curves which are similar but which indicate a slightly different rate of dye elimination were found for other animals.

Elimination of Dye Previous to Chloroform Anesthesia.—The colorimetric reading which was taken after the first minute interval varies in different dogs, since the concentration of dye is a function of the dilution of the dye in the total volume of blood which is in circulation. The higher the percentage concentration of the dye in the blood plasma with the same dose, the lower is the volume of plasma into which it is diluted. During the first minute after the injection, the dye is probably distributed fairly evenly through the circulation, if we assume

TABLE 2.—*Percentage Concentration of Rose Bengal in the Blood Plasma before and After Liver Injury by Chloroform Anesthesia*

Dog 22-40 (Adult Black and White Hound)*

	Colorimetric Readings and Values for R at Intervals of									
	One Minute,	2 Minutes		4 Minutes		8 Minutes		16 Minutes		
Date, 1922	Percentage	Percentage	R	Percent. age	R	Percent. age	R	Percent. age	R	Weight, Pounds	Plasma Volume, C.c.
3/28	61	56	0.92	46	0.76	31	0.51	26	....	22.8	662
3/29	61	57	0.95	49	0.81	31	0.52	31	....	22.5	662
3/31	64	61	0.95	41	0.64	..	....	30	....	21.5	622
4/ 2	Chloroform anesthesia 60 minutes										
4/ 3	78	72	0.93	63	0.81	53	0.67	46	....	19.8	512
4/ 4	91	86	0.95	(77)	(0.85)	(71)	(0.78)	(75)	0.86	19.3	438
4/ 5	89	83	0.94	80	0.90	77	0.86	63	0.70	18.8	450
4/ 6	..	81	....	69	....	57	....	50	....	18.0	....

* The dog was isolated on March 25 so that at the time of the anesthesia he had been fasted nine days. The experiment on April 3 was carried out six hours after the chloroform anesthesia. On April 3 and 4, the dog was quiet, drank a good deal of water but did not vomit. Clinically he was moderately toxic. The blood plasma was tinged yellow on April 3 and 4. The bracketed figures indicate that hemolysis accidentally occurred and that consequently the readings are somewhat inaccurate. The dose of rose bengal equals 30 mg. for each injection.

TABLE 3.—*Percentage Concentration of Rose Bengal in the Blood Plasma before and After Liver Injury by Chloroform Anesthesia*

Dog 22-41 (Gray Adult Police Dog)*

	Colorimetric Readings and Values for R at Intervals of									
	One Minute,	2 Minutes		4 Minutes		8 Minutes		16 Minutes		
Date, 1922	Percentage	Percentage	R	Percent. age	R	Percent. age	R	Percent. age	R	Weight, Pounds	Plasma Volume, C.c.
3/17	72	60	0.83	35	0.49	24	0.33	20	0.28	40.0	1,108
3/18	73	63	0.86	45	0.62	27	0.37	20	0.27	20.0	1,008
3/19	Chloroform anesthesia 45 minutes										
3/20	83	74	0.89	67	0.81	58	0.70	47	0.57	37.5	905
3/21	89	87	0.98	83	0.93	71	0.79	59	0.66	....	902
3/22	89	85	0.96	77	0.87	66	0.74	58	0.65	....	902
3/24	90	79	0.88	68	0.76	49	0.54	40	0.44	37.5	800
3/27	..	80	....	62	....	48	....	..	....	....	....

* On March 20 and 21 the dog was quiet, drank a good deal of water but he did not vomit. On March 20 the blood plasma was very dark yellow and progressively less so on the subsequent days. The dog fasted for a period of five days prior to the period of anesthesia. The dose of rose bengal equals 30 mg. for each injection.

TABLE 4.—*Percentage Concentration of Rose Bengal in the Blood Plasma before and After Liver Injury by Chloroform Anesthesia*

Dog 22-37 (Adult Male Bull Terrier)*

	Dose of Rose	Colorimetric Readings and Values for R at Intervals of													
		1	2		4		8		16		32		46		
Date	Bengal, Mg.	Minute, %	Minutes %	R	Minutes %	R	Minutes %	R	Minutes %	R	Minutes %	R	Minutes %	R	Weight, Pounds	Plasma Volume, C.c.
1922																
2/15	30	104	98	0.98	70	0.73	54	0.52	32	0.31	..	....	..	....	24.8	584
2/16	30	98	72	0.78	65	0.70	47	0.49	29	0.31	..	....	..	....	24.0	431
2/16	Chloroform anesthesia 55 minutes															
2/17	20	71	85	1.12	63	0.88	66	0.92	59	0.83	..	....	..	....	23.8	374
2/18	20	..	77	....	66	....	61	....	57	....	47	....	37	....	23.5	....
2/24	20	71	64	0.91	53	0.75	41	0.58	31	0.44	18	0.26	12	0.17	....	370
2/26	20	70	65	0.90	52	0.75	38	0.55	27	0.38	..	....	..	....	22.0	383
3/ 2	30	94	84	0.90	68	0.73	52	0.56	37	0.28	..	....	..	....	....	....

* On February 17, the plasma was strongly tinged with bile, less so on February 18, and not at all on February 24. The dog was quiet and drank a good deal of water on the two days following chloroform anesthesia. Food was withheld for five days previous to the anesthesia.

that this dye behaves in a manner similar to the "vital red" which is used for the estimation of plasma volume. During this first minute there probably is some elimination of the dye, but it is probably small. A small interval of time for the even distribution of the dye through the circulation must be given, and some arbitrary time shortly after the injection for the first determination of dye concentration must be taken. The interval of one minute may introduce an inaccuracy with regard to the actual computed plasma volume, but the exact unit of time taken before the first sample of blood is withdrawn is immaterial, provided it is of short duration and constant for each curve that is made. Great care was exercised to ensure that each sample was drawn exactly on time. This was particularly necessary in the case of the one minute samples, since a few seconds' delay in the drawing of the sample will introduce a definite error.

It will be seen from the estimation of the fifth sample of blood, taken sixteen minutes after the injection of the dye, that the rose bengal has largely disappeared from the blood stream. (The colorimetric readings varied between 20 and 30 per cent.) This concentration of dye is about the lowest which can be estimated with any degree of accuracy in the Hellige colorimeter and denotes a very pale plasma.

Elimination of Dye After a Period of Chloroform Anesthesia.—In these experiments, the animals were put under chloroform anesthesia for periods of time as indicated in the respective tables. The period of fasting previous to the day on which the animal was subjected to the chloroform anesthesia is given at the foot of each respective table. It is recognized that there is a definite relationship between the period of fasting and the extent of liver injury. The clinical effects of the anesthesia are indicated in each table, but these were not marked, and all of the animals recovered.

The first immediate effect of the liver injury by chloroform apparently is a fall in the plasma volume, since the concentration of dye in the plasma of the first sample was found to have increased. This is a constant finding in all of the experiments. All animals were sufficiently supplied with water, of which they freely partook after the period of chloroform anesthesia. The results therefore can hardly be explained on the basis of an insufficiency of water. It is possible that the increased thirst of the animals is the result of a decrease in the plasma volume. It is recognized that this dye is not as satisfactory for blood volume work as are the commonly used vital red dyes.

The second effect is a decided lag in the elimination of the dye, and the dye elimination curve becomes more nearly horizontal. The effect of chloroform anesthesia on the elimination of dye is not dependent on the elapse of a considerable interval of time after the anesthesia. The first estimation of dye elimination (Table 2) was made six hours after

the chloroform anesthesia, and shows a decided lag. The high values for the ratios corresponding to the eight and sixteen minute time intervals subsequent to the injection of the dye show a marked contrast to the values which were obtained before the liver injury had been induced (Tables 1, 2, 3 and 4). This point is of particular significance, for, as has been pointed out previously, it indicates that the injury of the liver is intimately concerned with the elimination of the dye. Subsequent determinations which were made on the same dog on successive days after the liver injury had been induced show a gradual return to the normal type of curve, although in several instances the experiments were not prolonged over a period of time sufficient to lead to a complete recovery. Recovery from the effects of the liver injury took place in all four experiments, hence pathologic material confirming the extent of liver injury was not available, but

TABLE 5.—*Percentage Concentration of Rose Bengal in the Blood Plasma before and After Liver Injury by Chloroform Anesthesia*

Dog 22-40.

	Colorimetric Readings and Values for R at Intervals of									
	One Minute,	2 Minutes		4 Minutes		8 Minutes		16 Minutes		
Date, 1922	Per-centage	Per-centage	R	Per-cent. age	R	Per-cent. age	R	Per-cent. age	R	Weight, Pounds	Plasma Volume, C.c.
4/17	70	..	....	54	0.78	40	0.58	33	0.47	18.8	575
4/19	64	60	0.94	51	0.80	36	0.56	30	0.47	19.0	625
4/21	Chloroform anesthesia 90 minutes										
4/22	76	78	1.06	82	1.06	76	1.00	63	0.83	18.0	526
4/23	93	107	1.16	94	1.02	89	0.96	87	0.94	17.5	432
4/25	86	79	0.91	73	0.85	64	0.75	51	0.60	17.0	470
4/26	77	73	0.95	66	0.85	54	0.70	48	0.66	16.0	517
4/26	Dog killed under ether and necropsy performed. Dose of rose begal equals 30 mg. for each injection										

the presence of bile pigments in the plasma indicated that definite injury had taken place. On account of lack of data, no attempt will be made in this paper to draw any correlation between the amount or extent of liver injury and the specific change in the curve of elimination that results from such injury. It is regretted that sufficient time was not available to obtain data on this point. Further work is necessary on many aspects of the problem.

Table 5 shows a more profound effect of chloroform anesthesia which was continued for a period of ninety minutes. The dog was sacrificed under ether in a moribund condition, and sections of the liver tissue showed a marked necrosis involving nearly all of the liver parenchyma. Yet even in this case there appears to be a tendency for the curve of elimination to return to normal.

Necropsy Notes (Table 5): Macroscopic examination showed a marked liver necrosis which was more marked in some areas, less so in others. The perilobular connective tissue was prominent and of a

pearly gray color. The liver parenchyma was gray and opaque. The gallbladder contained dye stained bile. The duodenum showed a considerable enteritis with reddish longitudinal streaks in the mucosa, which was denuded over small areas. There was a moderate amount of dye in the entire intestine. The blood of the animal was not clotted (necropsy performed some hours after death). There were 200 c.c. of serosanguineous fluid in both chest cavities. Microscopic examination of the liver showed an extensive liver necrosis involving most of the liver parenchyma; in some areas almost the entire liver lobule was destroyed, in others, the liver cells were swollen and granular.

Comment.—From the data obtained in these experiments, the plasma volume can readily be calculated. If we consider that the mixing of the dye with the blood is complete after one minute, and that the amount of dye which is eliminated during that time is not yet sufficient to alter appreciably its concentration in the blood, and we find that the percentage concentration of the dye in the plasma, after the injection of 30 mg. is, let us say, 58.7 per cent. in terms of the 0.0075 per cent. standard, it is easy to calculate the volume to which this dye has been diluted. The following equation may be deduced to express the plasma volume:

$$\text{Plasma volume} = \frac{\text{Milligrams of dye injected} \times 10^5}{\text{Colorimeter reading} \times 75}$$

The plasma volume determinations are given in each table and are calculated with the aid of the foregoing formula.

EXPERIMENT ILLUSTRATING QUANTITATIVE ELIMINATION OF DYE IN BILE FOLLOWING INJECTION INTO CIRCULATION

An attempt was made to determine the rate of elimination of the dye through a bile fistula, following its injection into the circulation. A temporary fistula was established (Table 6), and the collection of normal bile was continued for five hours. During the first half hour following the operation no bile was secreted into the collecting bag, but during the subsequent four and one half hours 10.5 c.c. were collected. Thirty milligrams of the dye were injected into the jugular vein, and collections of bile were made hourly. It was noted that the bile flowing through the glass cannula was definitely tinged with the dye eighteen minutes after the injection had been made. In another dog the time of appearance of the dye in the bile at the body wall, where it was first visible, was eight minutes. Evidently the dye is rapidly eliminated from the blood, but it continued to appear in the bile of the dog for as long as five hours, which is the longest period of observation. The samples of bile which were collected hourly after the injection of the dye were compared with a standard solution of the

dye, to which a few drops of the normal bile, collected during the period prior to the injection of the dye, were added. These readings were made in a Duboscq colorimeter, and considerable care was taken to ensure a perfect color match between the two solutions. This process was tedious and empirical, for it was impossible to calculate the exact amount of bile which must be added to the standard in order to secure the exact shade demanded by the specimen of colored bile which was obtained after the injection. During five hours of collection, 13 mg. of the 30 mg. which had been injected were recovered.

Following the injection of the dye, blood samples were withdrawn after one, two, four, eight and sixteen minutes, as in the previous experiments, and the percentage concentration of the dye in the plasma compared with the 0.0075 per cent. solution of the dye was determined. The curve corresponds to the normal type of curve which was obtained in the other dogs. The amount of dye which was removed from the

TABLE 6.—*The Quantitative Elimination of Rose Bengal in the Bile*

Time	Time Interval, Hours	Amount Collected, C.c.	Dye Eliminated, Mg.
*9:30 to 2:30	5	10.5	* .....
2:30 to 3:30	1	4.0	1.864
3:30 to 4:30	1	4.5	5.201
4:30 to 5:30	1	4.15	4.016
5:30 to 6:30	1	0.75†	0.491
6:30 to 7:30	1	2.2	1.470

* At 2:30, 30 milligrams of dye were injected.
† Most of the 5:30 to 6:30 sample was accidentally lost.
Total dye elimination equaled 13.042.

circulation by the taking of blood samples cannot possibly have had any material effect on the quantitative determinations in the bile.

At first sight it may appear that the dye itself possesses a cholagogue action, but when the many other factors which accompany this type of experiment and which may modify the secretion of bile are considered, one will hesitate to attribute the increased flow of bile to the action of the dye itself.

DISCUSSION

From the foregoing experiments, it appears that the elimination of rose bengal from the circulation is profoundly affected by injury of the liver, when this injury is induced through the agency of chloroform. With the experimental data at hand, it is impossible at this time to draw a correlation between the amount of liver injury and the extent of the change in the rate of elimination of the dye, and one would not be justified in claiming on the basis of the information thus far obtained that this method of experimentation will give any index of the activity of the liver in any one of its numerous and complicated functions.

From a study of the elimination of rose bengal from the blood streams of a large number of cases, it should be possible to determine the time limits which are required to reduce the concentration of dye in the blood stream to an indefinite amount. A lag in the elimination of dye from the blood stream can then be determined. This may give an index of the liver injury, or, if the term be permitted, of liver function.

CONCLUSIONS

Rose bengal, when injected into the circulation of normal dogs, at a dosage of about 20 mg. per 20 pounds (9.7 kg.) of body weight, remains in the blood stream for at least sixteen minutes.

Examination of samples of blood which were withdrawn from the circulation at definite specified intervals after the injection of the dye shows that there is a constant rate of elimination of the dye. The percentage concentration of the dye in the plasma as determined at definite time intervals may be tabulated and a "normal" curve of elimination of the dye may be obtained.

Under certain conditions of liver injury, such as may be induced by chloroform, the curve of dye elimination is markedly influenced and indicates a slower elimination of dye.

THE BASAL METABOLISM DURING PREGNANCY AND THE PUERPERIUM *

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The literature of normal pregnancy affords, so far as we are aware, no series of observations on the basal metabolism beginning with early pregnancy and continuing through the puerperium. Magnus-Levy,[1] in 1904, and Hasselbach,[2] in 1912, each reported a single case observed before conception and during pregnancy. Leo Zuntz,[3] in 1910, reported two cases with observations beginning in the fourth to the sixth months and continuing to delivery, and a third case in which observations were made in the sixth month only.

Magnus-Levy found both an absolute and relative increase in the oxygen consumption per unit of weight as early as the third month of pregnancy. Zuntz and other observers, however, found no increase in the oxygen consumption per kilogram, or, if any occurred, it appeared only late in the gestation period. Carpenter and Murlin,[4] in 1911, showed that the curve of total energy production of mother and child suffered no deflection at birth. They found that "the extra metabolism of the pregnant woman at the culmination of pregnancy, due in part to the accessory structures as well as to the fetus, is just equalled by the extra metabolism set up in the new-born child by exposure of its body to the outside world, and in the mother by the activity of the mammary glands," etc. The energy metabolism expressed per unit of weight of the pregnant woman was 7 per cent. less than that of the same woman newly delivered, and about 4 per cent. more than that of women in complete sexual rest. They concluded that the energy metabolism of the pregnant woman expressed per unit of surface is specifically higher than that of a woman in complete sexual rest, probably because of a higher metabolism in the uterus and because of a more rapid conduction of heat through the abdominal wall.

Baer[5] reported, in 1921, a series of forty-four patients with basal metabolism determinations at various periods during the last six weeks of pregnancy and the first eleven days postpartum. He compared the results obtained with the Aub and DuBois standards based on surface

* From the Nutrition Laboratory of the Carnegie Institution of Washington.

1. Magnus-Levy: Ztschr. f. Geburtsh. u. Gynäk. **52**:116, 1904.
2. Hasselbalch: Skand. Arch. f. Physiol. **27**:1, 1912.
3. Zuntz, L.: Arch. f. Gynäk. **90**:452, 1910.
4. Carpenter, T. M., and Murlin, J. R.: The Energy Metabolism of Mother and Child Just Before and Just After Birth, Arch. Int. Med. **7**:184 (Feb.) 1911.
5. Baer, J. L.: Am. J. Obst. & Gynec. **2**:1, 1921.

area. A total of 127 determinations were made, of which fifty-two were prepartum and seventy-five postpartum. From these figures expressed in percentage plus or minus, he constructed a chart showing on the average an increase from + 26 per cent. in the thirty-sixth week to + 33 per cent. in the fortieth week of pregnancy, and a decline from + 15 per cent. on the third day postpartum to + 1.4 per cent. on the eleventh day. No individual records are shown. He also suggested the use of basal metabolism determinations in diagnosing fetal death or the presence of twins.

Cornell,[6] in a more recent study of eighty-four cases, found the basal metabolism subject to many influences and the results of no value in practical obstetrics.

The results of Baer and Cornell were obtained on a series of patients, including many pathologic cases. Furthermore, the average number of observations per patient in both series is less than three, including prepartum and postpartum periods. Lack of control of psychologic factors is admitted by Cornell. The need for a long series of observations on individual patients during pregnancy and the puerperium is clearly indicated.

This study of a single subject is here reported because observations beginning in the fifteenth week of pregnancy have been continued at short intervals until the eighth week after delivery in the case of an extraordinarily normal pregnancy in which psychologic and physical factors exerting an untoward influence on the determinations were not present. So far as we are aware, no series of observations on normal pregnancy comparable in frequency and length of period covered have been reported previously.

SUBJECT

The subject of these observations was a normal primipara, aged 29 years, four and one-half months, at the beginning of pregnancy. The date of the last menstruation was Oct. 22, 1921. Morning nausea and vomiting occurred during the third month but not thereafter. No febrile complications arose at any time during pregnancy or the puerperium. Indeed, the buccal temperature never exceeded 99 F. even on the day of delivery. Edema of the ankles was present one day during the second month and was constantly present during the last three months, though varying in amount. Thus, on rising in the morning little or no pitting edema could be detected, although a considerable degree of edema was present in the evening. The high pulse rate deserves some comment. Frequent examinations over a period of from eight to ten years had always shown an unusually high rate: from 85 to 90. She had enjoyed moderately strenuous athletics, swimming, canoeing,

6. Cornell, E. L.: Surg., Gynec. & Obst. **36**:53, 1922.

hockey, etc., for years without any evidence of cardiac weakness. During pregnancy she was able to carry on her usual activities with practically no limitation. Physical examination revealed no evidence of cardiac damage. The increase in the vital capacity is itself good evidence of the normal cardiac condition.

Labor pains were first felt about 1 a. m. on July 31. During one and one-half hours in the first stage, self-administered nitrous oxid relieved the intensity of the pains, and in the second stage under ether anesthesia, delivery was hastened by the application of low forceps by Dr. R. C. Cochrane. Birth of a girl baby occurred at 11:30 a. m., July 31, after ten and one half hours' labor. After a hospital stay of two weeks and three days, she returned to her home. During the first two weeks of the puerperium she was in bed, then followed two weeks of gradually increasing activity, and the resumption of nearly normal activity at the end of a month.

METHODS

A Benedict portable respiration apparatus was used, and the observations were made approximately at two weeks intervals at the patient's home, with the exception of the first two following delivery, which were made in the New England Baptist Hospital. During the last three weeks of pregnancy, observations were made weekly. The same apparatus was used throughout the entire period of observation. The usual precautions as to the omission of food for twelve hours and absolute rest in bed for at least one-half hour preceding tests were observed.

On the night before a test day, the subject's weight was taken at 10:30 p. m., and she went to bed at about 10:45 p. m. She arose at 6:30 a. m. to urinate and to be weighed and then returned to bed, often sleeping until the arrival of the operator at 8 a. m. While in the hospital, the determinations were made when she was still confined to bed, and hence no activity intervened between the night's rest and the test, with the exception of such activity as was involved in nursing the baby at 6 a. m. Careful notes were made as to the rare instances of nervousness on the part of the subject and of any possible cause for disturbance. During the later months fetal movements occurring during the periods were recorded. The subject reported that at almost all hours of the day slight movements could be felt if her attention was not focused on other matters; hence only unusual movements were recorded. On one occasion, such movements occurred following the first period, and consequently the second period was delayed until the activity had subsided.

So far as extraneous movements on the part of the subject, such as turning on the side, raising the hand, or changing the position of the

feet, are concerned, it may be definitely stated that none occurred during the metabolism tests. The reasons for such cooperation were: first, the extraordinary composure and self-control of the subject; second, the exercise of great care in making the subject comfortable before beginning experiments; and third, the intelligent understanding on the part of the subject of the nature of the test being carried out.

Observations were always made in three ten minute periods. Tests for leakage of the apparatus and connection with the mouth were made during each period according to a new technic. Such tests were invariably negative and demonstrated the absence of a leak.

DATA

In Table 1 are given the data of the metabolism experiments which may be referred to, and in Figure 1 are given the curves for the metabolism, body weight, pulse rate, and vital capacity.

We first call attention to column 5, Table 1, showing the total basal calories per twenty-four hours. The average of the first three determinations was 1,269 calories, with which, in the absence of observations preceding pregnancy, we must compare the metabolism at later dates. The total computed twenty-four hour basal metabolism steadily increased until on July 19 the computed metabolism was 23 per cent. greater than it was five months previously. This extraordinary increase in basal metabolism was accompanied by an increase in weight of but 14 per cent. It is clear, therefore, that the specific metabolism of the newly gained tissue must have been considerably higher per kilogram than that of the subject before the increase in weight occurred.

This increase in metabolism is out of all proportion to the increase in metabolism which would occur in a normal woman of the same age and height with a similar gain in weight. Thus, the normal woman, according to the table of Harris and Benedict, of the same age and height would gain in metabolism only 5 per cent. with a similar gain in weight. According to the prediction tables of Aub and Du Bois, the gain in metabolism under the same conditions would be 5 per cent. It is clear, therefore, that the gain in basal metabolism of the pregnant woman, as she gains in weight, is at a different rate, at least in the later months of pregnancy, from that shown by the normal woman by the standard prediction tables.

Following delivery, the patient's weight remained fairly constant, yet marked changes in the basal metabolic rate were observed. The total basal calories fell rapidly during the first three weeks after delivery to the lowest level observed at any time during the eight months, 9.6 per cent. below the level during the third month of pregnancy.

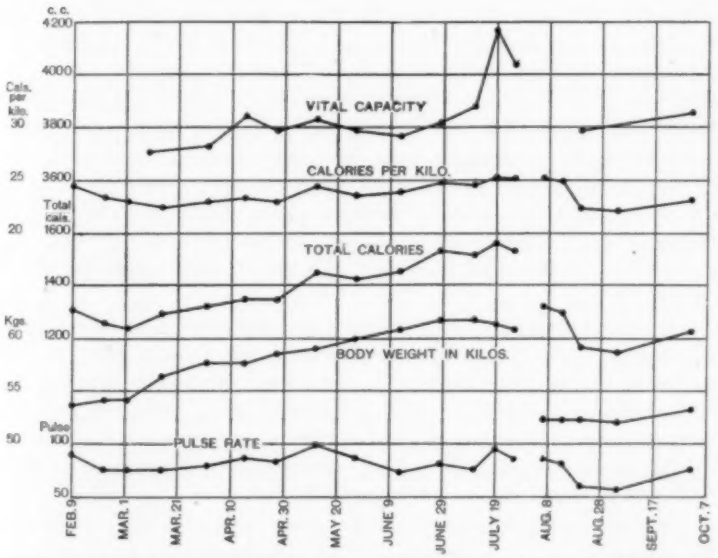
We regard this comparison of the patient herself against herself at different periods as of greater importance than a comparison of the

TABLE 1.—*Computed Basal Metabolism* *

Date, 1922	Oxygen per Minute, C.c.	Pulse	Body Weight (Nude), Kg.	Computed Calories per 24 Hours	Deviation from H. and B.† Standard, Percentage	Calories per Kg. per 24 Hours	Increase in Calories per 24 Hours Over Average of Feb. 9 to March 2 Percentage
Feb. 9	188	90	53.6	1,308	—1.5	24.4	.....
Feb. 21	181	76	54.1	1,260	—5.4	23.3	.....
Mar. 2	179	76	54.1	1,240	—7.1	22.9	.....
Mar. 15	187	76	56.4	1,297	—4.2	22.4	+ 2.2
April 1	190	80	57.7	1,321	—3.3	22.9	+ 4.1
April 15	194	87	57.7	1,347	—1.3	23.3	+ 6.1
April 27	194	84	58.6	1,347	—1.6	22.9	+ 6.1
May 12	208	99	59.1	1,448	+5.2	24.4	+14.1
May 27	204	87	60.0	1,421	+2.6	23.6	+12.0
June 13	209	74	60.9	1,454	+4.4	23.9	+14.6
June 28	221	82	61.8	1,530	+9.5	24.8	+20.6
July 11	218	77	61.8	1,514	+8.2	24.6	+19.3
July 19	235	96	61.4	1,561	+12.1	25.3	+23.0
July 26	221	87	60.9	1,530	+10.1	25.2	+20.6
July 31 delivery							
Aug. 6	190	87	52.3	1,321	+0.7	25.2	+ 4.1
Aug. 13	187	82	52.3	1,301	—0.9	24.9	+ 2.5
Aug. 20	168	61	52.3	1,167	—11.5	22.3	— 8.9
Sept. 3	165	58	52.0	1,147	—12.9	22.1	— 9.6
Oct. 1	177	76	53.2	1,227	—7.5	23.0	— 3.3

* All the metabolism figures reported in this paper were based on the revised methods of calculation resulting from a critical test by Dr. T. M. Carpenter of the Nutrition Laboratory of this portable apparatus (by burning known amounts of alcohol) and represent most accurate measurements of the oxygen consumption.

† "H. and B." is an abbreviation for Harris and Benedict, Carnegie Institution, Washington, Pub. No. 279, 1919, Tables 3 and 4, pp. 260 et seq.



Curves for pulse rate per minute, body weight, basal heat production per twenty-four hours and per kilogram per twenty-four hours, and vital capacity from the fifteenth week of pregnancy until the eighth week after delivery (July 31, 1922).

pregnant woman at any given stage with a nonpregnant, standard, normal woman of like age and weight. However, such comparison is of some interest, and, accordingly, under Column 6 in Table 1 are given the percentage deviations from the standard prediction of Harris and Benedict for normal women of the same age, height and weight. It may be stated that the predictions of Aub and Du Bois closely paralleled those of the Harris and Benedict tables at all stages, showing an average difference of but forty-seven calories. Accordingly, the percentage deviations from their predictions are but slightly different.

These figures for percentages plus or minus standard predictions stand in strong contrast with the results obtained by Baer. His forty-four patients averaged from + 26 per cent. in the thirty-sixth week to + 33 per cent. in the fortieth week, using the Aub and DuBois standard for comparison. He made, however, only fifty-two determinations on forty-four patients from the Michael Reese Maternity Clinic, of whom eighteen were primiparae. It was difficult under these circumstances to eliminate psychologic and other factors, which might produce considerable increases in the metabolic rate.

It is pertinent at this point to comment on certain factors affecting the metabolism in pregnancy. Diurnal variation in the basal metabolism of a man undergoing a prolonged fast has previously been reported from this laboratory.[7] A similar lowering of the metabolism was observed on one occasion during these observations. On March 15, the subject slept during the third period, and her oxygen consumption decreased by 9 per cent. during this period. Since our object was to secure data comparable with standards which have been derived from observations on the waking state, this period was not used in making up our average. However, it agrees with other observations from this laboratory in indicating a lowering of approximately 10 per cent. in the metabolism during sleep, and suggests that only during sleep can the maximum relaxation required for a true "basal" determination be secured.

Another important factor affecting the metabolic rate, especially in primiparae, is the degree of mental relaxation. On February 9, both the pulse rate and the oxygen consumption were higher than for the next three determinations. The subject denied any feeling of nervousness, and appeared quite comfortable, but it is probable that the newness of the experience was disturbing, nevertheless. Single observations under these circumstances are open to doubt.

During the last six weeks of pregnancy, evidence was obtained of the existence of factors influencing the metabolism much more markedly. On June 28 and July 26, the second of three periods each gave figures for oxygen consumption much greater than the first and third.

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7. Benedict, F. G.: Carnegie Inst. Wash. Pub., No. 203, 1915, p. 337.

The discrepancies were noted at the time, and every effort made to find an explanation. By a new technic a test for tightness of the apparatus was made during the progress of every period, and in both these instances no evidence of leakage could be found. Further tests for leakage were made at the end of these periods, without result. The same stop-watch was used throughout. In short, we have no reason to suspect the apparatus or the timing of the periods. The subject denied experiencing any discomfort or any unusual sensations. No unusual fetal movements were felt. It appears, therefore, that the occurrence of brief periods of greatly increased metabolism during the latter part of pregnancy must be accepted until definite proof to the contrary is produced.

The interpretation of such variations would seem to depend chiefly on the assumption that great variations in fetal activity may occur without corresponding disturbance of the mother. The significance of kymograph records purporting to give evidence of the character of

TABLE 2.—*Variations in Consumption of Oxygen*

Date	Period	Oxygen Consumption, C.c.	Pulse	Time, a. m.
June 28	I	220	85	8:17
	II	242	88	8:39
	III	221	78	8:57
July 26	I	228	90	8:25
	II	279	97	8:42
	III	218	88	9:02

fetal movements has been questioned by such authorities as Williams.[8] There seems to be no definite knowledge as to the nature and metabolic influence of fetal movements. However, no better explanation for these figures is at present available. These periods, however, were not regarded as basal and accordingly were not used in the averages.

Three other factors possibly influencing the basal metabolism in pregnancy may be mentioned. The first of these is seasonal variation. The early months of pregnancy occurred in the winter, whereas the later months and the puerperium occurred in midsummer. No evidence of any seasonal influence is obtainable from the data.

Hasselbalch [9] found slight acidosis present during the last weeks of pregnancy in his subject. It is possible that slight acidosis, as shown by lowered plasma carbon dioxid combining power may accelerate the basal metabolism.

Hypertrophy of the thyroid is frequently observed during pregnacy, and many writers have spoken of a compensatory hyperactivity

8. Williams, J. W.: Obstetrics, New York, D. Appleton & Co., 1922, p. 163.
9. Hasselbalch: Skand. Arch. f. Physiol. **27**:1, 1912.

of the thyroid at the time. Neither hypertrophy of the thyroid nor any constant increase in pulse rate appeared in this subject, and consequently no objective evidence can be brought forward indicating any special influence on the part of the thyroid.

The curve of calories per kilogram is an instructive one. From February 9 until April 27 it is fairly constant; but from April 27 until July 26 it shows a striking rise from 22.9 to 25.2 calories per kilogram. Fluctuations in body weight during this time were greater than during the early part of pregnancy. Thus the average difference in weight between weights taken at 10 p. m. and 6:30 a. m. from July 20 to July 26 was 2.6 pounds (7257.4 gm.), whereas in February the average difference in these weights for a corresponding period was 1 pound (4535.9 gm.). The warmer weather, disappearance of edema during the night, and the increased metabolism no doubt influenced this fact. It should be said, however, that practically all edema of the extremities had disappeared in the morning when the metabolism tests were made, and the curve of weights taken at this time is an extraordinarily regular one.

During the first two weeks of puerperium, the heat production fell slightly, to 24.9 calories per kilogram, and at the end of the third week, the rate was 22.3 calories per kilogram.

In any consideration of the heat production per kilogram during pregnancy, gain in adipose tissue is important. Of Zuntz's three patients, two gained weight independently of the products of conception. Magnus-Levy's patient was a giantess who apparently did not gain in adiposity. It is not clear from the paper of Carpenter and Murlin whether their three patients had gained adipose tissue during pregnancy or not. Our subject weighed, one week after delivery, 1.3 kg. more than she did before conception. Such a difference may well be accounted for as due to increased mammary and uterine tissue, and certainly does not indicate such a gain in adipose tissue as would influence the heat production per kilogram. The difference in weight between that of five days before delivery and one week after was 8.6 kg., which may be compared with an average loss of 7.257 kg. between the thirty-ninth or fortieth week and the third day postpartum reported by Baer. This difference may be analyzed as follows:

TABLE 3.—*Elements Causing Increase in Weight Before Delivery*

	Kg.
Baby	2.8
Placenta	0.8 (approximately)
Liquor amnii	1.0 (approximately)
Uterine increase	1.0 (approximately)
Total	6.6

Approximately 2 kg. remain unaccounted for, which probably consisted of edema. The metabolically active tissue lost at delivery consists of the child, the placenta and that portion of the uterus which is lost during involution. The approximate weight of these tissues was 5.6 kg. The difference between the twenty-four hour basal metabolism five days before delivery and six days after was 209 calories. The metabolic rate for baby, placenta, and uterus just before delivery would accordingly seem to have been about 37 calories per kilogram. It is of some interest to compare this estimate with the observed minimum metabolism of new-born infants reported by Benedict and Talbot,[10] who found an average of 42 calories per kilogram as the minimum metabolism of 105 new-born infants.

In the following tables are given such figures for the oxygen consumption reported by other writers as were found.

TABLE 4.—*Oxygen Consumption per Kilogram of Body Weight Per Minute* *

Condition	Authors' Case, C.c.	Magnus-Levy, C.c.	Zuntz (A) C.c.	Zuntz (B) C.c.	Zuntz (C) C.c.	Carpenter-Murlin (1) C.c.	Carpenter-Murlin (2) C.c.	Carpenter-Murlin (3) C.c.	Hasselbalch, C.c.
Normal.....	....	2.79	3.47	3.50	3.75	....	....	....	....
During 3d mo..	....	2.88	....	....	....	....	....	....	....
During 4th mo..	3.45	2.92	....	....	3.72	....	....	....	....
During 5th mo..	3.30	3.16	....	3.65	3.54	....	....	....	....
During 6th mo..	3.33	3.14	3.88	3.52	....	....	....	....	....
During 7th mo..	3.42	3.10	....	....	....	....	....	....	....
During 8th mo..	3.42	3.20	....	3.92	3.45	....	....	....	....
During 9th mo..	3.59	3.33	....	3.75	3.47	3.4	3.9	3.4	2.98
Weight (nude) before delivery, kg.	60.9	115.1	....	58.04	67.8	63.0	58.0	68.2	76.3
Puerperium—									
1st week.....	3.64	....	....	....	....	....	....	....	....
2d week.....	3.56	....	....	....	....	....	4.12	3.34	....
3d week.....	3.22	....	....	....	....	3.46	....	....	....
4th week.....	3.18	....	....	....	....	....	....	....	2.85
5th week.....	....	....	....	....	....	....	....	....	2.70
8th week.....	3.32	....	....	....	....	....	....	....	2.96

* All values are computed to 0 C. and 760 mm. and previous to delivery are averages obtained from observations on two or more days.

The only patient who did not show a higher oxygen consumption in the later months of pregnancy than in earlier months was Zuntz's Patient C. She had acute pyelitis with fever in the fifth month and thereafter gained much weight. He calculated that she gained 7 kg. in fat alone. His Patient A actually weighed less at term than before conception. This strongly suggests some abnormality and perhaps invalidates the comparison of the oxygen consumption in the middle and at the end of pregnancy.

The influence of obesity on the oxygen consumption per kilogram of body weight is well shown by the figures given above. Thus, in the ninth month, the lowest oxygen consumption is found in the case of

10. Benedict, F. G., and Talbot, F. B.: Carnegie Institution Washington Pub. No. 233, 1915, p. 99.

the patient of Magnus-Levy, whose weight at this time was 115.1 kg. The highest oxygen consumption per kilogram per minute is seen in the case of the second patient of Carpenter and Murlin, whose body weight was the least of all cases here shown.

Our observations do not confirm those of Carpenter and Murlin in finding a higher energy production per kilogram during the puerperium than in the ninth month of pregnancy. The first impression gained by examining the first column of Table 4 is that the oxygen consumption at the end of the first week of the puerperium is greater than that during the ninth month. However, this figure, 3.64, was obtained on a single date, whereas the figure 3.59 represents the average of four different observations. On consulting Table 1, it is clear that the highest metabolism per kilogram of body weight occurred on the eleventh day before delivery. If the two highest figures during the puerperium are compared with the last two observations during pregnancy, again the higher basal rate is observed during pregnancy. The average calories per kilogram per hour for the four weeks preceding delivery was 1.08 as against 1.03 for the four weeks after delivery. In all three of their patients, a decided increase in the calories per hour per kilogram occurred during the peurperium as compared with observations made from one day to three weeks preceding delivery. The average increase was 7 per cent. They suggested that the process of involution set free decomposition products which stimulated the general heat production. Hyperactivity of the sweat glands and the activity of the mammary glands were also considered as explanations. It may be pointed out, however, that although no fever was present at the time of metabolism determinations the clinical charts of these patients show in each case afternoon temperatures, on several occasions taken by mouth, ranging from 99 to 100 F. While these temperatures are not considered clinically pathologic, they represent a considerable variation from the temperature curve of the present subject which did not rise above 99 F. at any time during the peurperium. During the first two weeks the basal metabolism showed only a slight downward tendency, but by the third week it had fallen to a point lower than at any time during pregnancy, both total and per kilogram. This low level was found at the end of the fourth week, but eight weeks after delivery, with a slight increase in body weight, the oxygen consumption rose somewhat, possibly in part due to a considerable increase in diet on the part of the subject.

PHYSICAL MEASUREMENTS

We have called attention to the striking difference between the gain in basal metabolism by the pregnant woman in the later months of pregnancy and the gain in metabolism with a similar gain in weight on the part of the nonpregant woman. It is important that metabolism stand-

ards for pregnant women should be established. In the hope that our results may be more useful to other observers we submit Table 5 of physical measurements.

Before commenting on these results, some explanation of the method of measurement is necessary. Height was taken in stocking feet. The trunk length is the measurement recommended by Dreyer. The subject sat on a level surface with the back against a measuring rod. With the back of the knuckles on the floor the body was bent forward and raised and the sacrum thrust against the measuring rod. Then with the hands in the lap and the body erect, the height to the vertex was taken. Chest circumference was measured just below the mammary tissue and with the chest at rest; that is, neither at maximum inspiration or expiration. The interacromial diameter was taken by means of obstetric calipers and represents the distance between the tips of the acromion processes with the patient standing erect, the arms hanging at the sides. The anteroposterior chest diameter was also taken with obstetric calipers and represents the distance in the horizontal

TABLE 5.—*Physical Measurements*

	March 10, 1922	May 24, 1922	Oct. 5, 1922
Lengths—Height	162.4	162.4	162.7
Trunk	84.8	84.8	84.4
Diameters—Interacromial	.....	34.0	35.4
Chest, anteroposterior	.....	19.5	18.2
Chest, lateral	.....	26.0	25.0
Intercrestal	.....	28.5	28.6
Circumference—Chest	75.5	77.0	72.5
Weight	55.5	60.0	58.1

plane from the lower border of the sternum to the opposite spinous process. The lateral chest diameter was the maximum diameter between opposite sixth ribs taken in midaxillary line. These two chest diameters were taken with the chest at rest and are bony measurements, the points of the calipers being approximated to bony surfaces as nearly as possible. The intercrestal diameter was also taken with obstetric calipers and represents the maximum diameter between the outer lips of the iliac crest.

One purpose in taking these measurements was to determine whether measurements which have been recommended as standards for weight prediction would vary with the change of weight during pregnancy. It is obvious that the measurements of length, which are essentially bony measurements, show no variation. Slight variation appears in the diameters, with the exception of the intercrestal diameter. The correlation between the intercrestal diameter and normal weight should be studied with a view to determining its usefulness in assessing normal weight. The largest variation appears in the chest circumference, which almost parallels the changes in weight. The close rela-

tion between the chest circumference and body weight, both in normal persons and in diabetic patients who are much overweight, has recently been shown by Gray and Root [11] and Root and Miles.[12] It is of some interest that this measurement also reflects the changes in body weight during pregnancy. No doubt the upward pressure of the pregnant uterus causes some flaring outward of the lower ribs, in which case the increase in diameter may be considered entirely mechanical rather than actually due to increase of soft tissues outside the ribs.

VITAL CAPACITY

Measurements were taken with the Benedict portable respiration apparatus with the subject standing robed in a loose gown. Five readings were taken, and the highest of the five recorded. Usually the third was the highest.

TABLE 6.—*Observed Vital Capacity Compared With Three Standards*

Date	Observed	Room Temperature, C.	West*	Peabody†	Dreyer‡ Prediction from		
					Trunk	Weight	Chest
March 10, 1922	3,710	....	3,160	3,060	3,250	3,305	3,497
April 1, 1922	3,731	22.0	3,250	3,060	.....	3,376	.....
April 15, 1922	3,841	19.8	3,250	3,060	.....	3,376	.....
April 27, 1922	3,790	20.0	3,260	3,060	.....	3,415	.....
May 12, 1922	3,852	18.6	3,274	3,060	.....	3,435	.....
May 27, 1922	3,790	20.2	3,286	3,060	3,290	3,473	3,675
June 13, 1922	3,770	19.1	3,306	3,060	.....	3,511	.....
June 28, 1922	3,820	22.5	3,324	3,060	.....	3,548	.....
July 11, 1922	3,880	21.7	3,334	3,060	.....	3,548	.....
July 19, 1922	4,170	27.0	3,320	3,060	.....	3,532	.....
July 26, 1922	4,040	21.1	3,306	3,060	.....	3,511	.....
Aug. 20, 1922	3,790	22.0	3,160	3,060	.....	3,147	.....
Oct. 1, 1922	3,856	22.8	3,130	3,060	3,245	3,184	3,397

* West, H. F.: Clinical Studies on the Respiration. VI. A Comparison of Various Standards for the Normal Vital Capacity of the Lungs, Arch. Int. Med. **25**: 306 (March) 1920.
† Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration, IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**: 443 (sept.) 1917.
‡ Dreyer, G., and Hanson, G. F.: The Assessment of Physical Fitness, New York, Paul B. Hoeber, 1921, p. 52 et seq.

The subject always exhibited a higher vital capacity than the standard shown, even two months after delivery. The latter fact eliminates pregnancy as the sole case for her hypernormal vital capacity and is in accord with the observation that persons with athletic training may have exceptionally high vital capacity.

The vital capacity curve during pregnancy was most striking. A slight but definite upward trend is apparent from the third to the eighth month, with a marked increase during the last month. That this was not a practice effect is indicated by the fall to the earliest level on August 20, three weeks after delivery. The reasons for this decided increase during the last month of pregnancy are not entirely clear. We

11. Gray and Root: Boston M. & S. J. **185**:28, 1921.
12. Root and Miles: J. Metab. Res. **2**:173, 1922.

have some evidence of an increase in chest volume from the chest measurements. Thus the circumference on March 10 was 75.5 cm., on May 24 it was 77.0 cm., and on October 5, two months after delivery, it was 73.5 cm. The chest diameters were also greater on May 24 than on October 5. Unfortunately, we have no chest measurements taken at the time of the highest vital capacity readings. A further suggestion as to the relation of an increased chest volume as an explanation of this high vital capacity comes from the fact that the greatest increase in vital capacity occurred during the period when the uterus descends somewhat into the pelvis, presumably releasing the upward pressure and allowing freer descent of the diaphragm.

An interesting possibility is based on the assumption that the vital capacity measures cardiac power and efficiency. It may be that during the last few weeks of a normal pregnancy the heart truly gathers its forces in preparation for the supreme test of labor, and that this increase in vital capacity is an evidence of this adaptive mechanism.

Hasselbalch found the vital capacity slightly greater in the last month of pregnancy than thereafter, and considered this fact due to the more complete emptying of the lungs and less residual air. However, the changes in lung volume were not great.

A comparison of the observed vital capacity with the standard predictions of West, Peabody, and Dreyer shows striking differences. The range of the standards is from 3,050 c.c. to 3,497 c.c. for the measurements of the subject observed on March 10, Dreyer's prediction from the chest circumference being much nearer to the observed 3,710 c.c. When the entire series of observations is compared with the predictions, again the Dreyer prediction from chest circumference seems the closest. It follows from the fact that weight and chest circumference have a high degree of correlation that the vital capacity predicted from the weight should vary somewhat as that predicted from the chest; and, in fact, Dreyer's prediction from weight does run parallel to the chest predictions.

SUMMARY

The course of the basal metabolism from the fifteenth week of pregnancy to the eighth week after delivery is reported in the case of a primipara in whom pregnancy was uncomplicated by gain in adipose tissue or disease of any sort. The basal metabolic rate during the fourth month was essentially that predicted by the standard for non-pregnant women of the same age, height and weight. From this time, a steady increase in the total calories per twenty-four hours was observed until eleven days before delivery, when the total basal metabolism was 23 per cent. greater than that during the fourth month. This increase in metabolism is out of all proportion to the increase in basal metabolism shown by standard prediction tables for normal

women with a corresponding gain in weight. The gain in basal metabolism expressed as calories per kilogram from the fourth month of pregnancy to the eleventh day before delivery was 7.6 per cent. Following delivery, although the subject's weight remained nearly stationary, the basal metabolism fell gradually to a point 9.6 per cent. lower than the rate observed during the fourth month of pregnancy.

The high metabolic rate during the last month of pregnancy only partially reflects the much higher metabolic rate of the fetus per unit of weight since the maternal weight is made up in part of inactive tissues such as edema and the fluid contained in the amnion. It appears from our computations that the metabolism of the fetus at term was approximately 37 calories per kilogram, whereas the basal metabolism of the mother was 23.5 calories per kilogram during the fourth month of pregnancy, and 22.1 calories per kilogram one month after delivery.

The vital capacity increased steadily from the fifth month onward with a marked rise in the last months of pregnancy.

CONCLUSIONS

1. A marked increase in the basal metabolism both in total twenty-four hour calories and in the calories per unit of weight occurs during the later months of pregnancy.

2. The heat production per unit of weight falls gradually during the first three weeks after delivery to a level lower than that observed during the fourth month of pregnancy.

3. Standards of basal metabolism for use in practical obstetrics should be developed by the study of normal pregnant women, and a comparison of the basal metabolism of pregnant women should not be made with standards of basal metabolism for nonpregnant women.

TOXIC NEPHRITIS IN PYLORIC AND DUODENAL OBSTRUCTION

RENAL INSUFFICIENCY COMPLICATING GASTRIC TETANY *

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The clinical, pathologic and biochemical changes resulting from obstruction in the upper intestinal tract have been carefully studied by a number of investigators. It is known that a marked or complete pyloric or duodenal obstruction results in severe toxemia or death. The associated increased nerve irritability and the development of a syndrome usually designated gastric tetany have long been recognized. Experimental work along these lines has been concerned chiefly with the nature of the toxic agent, with the changes in blood chemistry, and with the mechanism involved in the production of gastric tetany. The cause of death in this group of cases also has received much attention. Various hypotheses have been advanced, based on experimental studies and on theoretic considerations, but we believe that the associated renal lesion has not yet received sufficient recognition or consideration.

Clinically it has been observed that the body reacts differently to intestinal obstruction, depending on certain factors, such as: (1) the location of the obstruction, (2) the degree of the obstruction, (3) the acuteness of the process, and (4) individual susceptibility to the specific toxin involved as expressed clinically by increased nerve irritability, spasmophilia, vomiting, etc. It is possible also that the kidney may vary in susceptibility to injury, particularly in the presence of an existing disease.

We are attempting to show here that serious renal injury exists in many cases of duodenal and pyloric obstruction, particularly in cases exhibiting evidence of tetany. We are not attempting to controvert the importance of increased tissue catabolism in the production of a high level of blood urea, but wish to emphasize the importance of the renal lesion. The toxic injury sustained by the kidney is of grave consequence and is characterized by: (1) albuminuria and cylinduria; (2) marked functional impairment of the kidneys, associated with marked increase of total nonprotein nitrogen, of creatinin and of urea

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in the blood, and a definite decrease in phenolsulphonephthalein excretion; (3) a clinical syndrome due, in part at least, to renal insufficiency, and (4) a well-defined pathologic picture of toxic nephritis.

CLINICAL OBSERVATIONS AND EXPERIMENTAL DATA RELATIVE TO HIGH INTESTINAL OBSTRUCTION

Intestinal obstruction is less serious and runs a more chronic course with symptoms less acute, the lower the obstruction. The higher the block in the gastro-intestinal tract, the more fulminating are the symptoms and the more serious is the prognosis.

Among the hypotheses advanced to explain the causes of the clinical manifestations and death in upper intestinal obstruction are: (1) reflex nerve disturbance causing cardiac or vasomotor paralysis; (2) infection of the peritoneum and blood stream from increased permeability of the intestinal walls for bacteria; (3) failure for the opportunity for neutralization of toxins of the upper intestinal tract by substances in lower segments, and (4) the development of toxic substances in the proximal portion of the intestine and their systemic absorption. The last hypothesis seems worthy of much consideration.

In 1909, Draper [1] defined an "oral, lethal line" in the duodenum between the ampulla and pylorus. He says that ligation of the pylorus causes "physiological death" less often than lower occlusions. Whipple, Stone and Bernheim,[2] in 1914, using closed duodenal loops in dogs, showed rather conclusively that a toxic substance is formed, which when injected into animals produces a picture identical with that obtaining in the obstructed animal. As possible agents, they eliminated bile, gastric and pancreatic juice and certain toxic substances such as split-food products. They claim that the toxic substance is either formed in the duodenal mucosa or is a product of bacterial autolysis, or both. The removal of the duodenal mucosa prevents the formation of this toxic substance. Hartwell, Hoguet and Beekman,[3] in 1914, working along similar lines, came to somewhat different conclusions and maintained that it is lack of water absorption or excessive loss of fluid, in conjunction with elaboration of a cellular poison from a gangrenous duodenal mucosa which accounts for the toxemia and death in high intestinal obstruction. They emphasized the changes in the duodenal mucosa as of great importance. Dragstedt [4] and others believe

1. Draper, J. W.: Intestinal Obstruction: An Outline for Treatment Based upon the Cause of Death, Am. J. M. Sc. **137**:725-739, 1909.
2. Whipple, G. H.; Stone, H. B., and Bernheim, B. M.: Intestinal Obstruction. III. The Defensive Mechanism of the Immunized Animal Against Duodenal Loop Poison, J. Exper. M. **19**:144-165, 1914.
3. Hartwell, J. A.; Hoguet, J. P., and Beekman, F.: An Experimental Study of Intestinal Obstruction, Arch. Int. Med. **13**:701-736 (May) 1914.
4. Dragstedt, L. R., and Dragstedt, C. A.: Acute Dilatation of the Stomach, J. A. M. A. **79**:612-615, 1922.

that bacteria are essential for the production of the characteristic toxic substances. The splitting up of proteins produces a substance which causes the characteristic toxemia. Recently, Gerard [5] has suggested that histamin may be the toxic agent. Abel and his collaborators are at present investigating histamin and histamin containing albuminoses, and in all probability their work will shed some light on the nature of the toxic agent involved.

Werelius,[6] as the result of his work, questions the conclusions of Whipple and his associates and attempts to involve insufficiency of the liver as an etiologic factor in death following high intestinal obstruction. He questions whether the absorption of toxic products from the intestinal mucosa plays any part in causing death. He emphasizes the presence of white bile in the duodenum, of a lowered blood sugar level and an increased blood urea content as possible results of hepatic insufficiency.[7] Strangely, he failed to find an increase of carbon-dioxid carrying capacity of the blood.

The blood chemistry in high intestinal obstruction reveals much of interest. Wilson, Stearns and Janney [8] were the first to call attention to the presence of alkalosis in parathyroprival tetany. McCallum [9] and his associates and McCann [10] studied the relationship of tetany to pyloric closure and found that the plasma chlorids dropped sharply in this condition; that the alkaline reserve was definitely increased, and that the electrical reactions were heightened. The alveolar carbon dioxid was markedly increased, showing that there was no carbon dioxid retention in the blood. Their animals developed twitchings, convulsions and coma prior to death. It is difficult to determine whether the condition induced by these writers corresponds to that seen in this group of patients, owing to the lack of clinical details in their report. They noted that with the constant loss of gastric juice and its hydrochloric acid there ensues a decrease of the chlorids of

5. Gerard, R. W.: The Lethal Agent in Acute Intestinal Obstruction, J. A. M. A. **79**:1581-1584 (Nov. 4) 1922.

6. Werelius, A.: Is Death in High Intestinal Obstruction Due to Liver Insufficiency? J. A. M. A. **79**:535-539 (Aug. 12) 1922.

7. In hepatic insufficiency the urea nitrogen constitutes, as a rule, a decreased, rather than an increased percentage of the total nonprotein nitrogen. His explanation of the increased urea concentration does not seem convincing.

8. Wilson, D. W.; Stearns, T., and Janney, J. H., Jr.: The Excretion of the Acids and Ammonia After Parathyroidectomy, J. Bio. Chem. **23**:123-137 1915.

9. MacCallum, W. G.; Lintz, H.; Vermilye, H. N.; Leggett, T. H., and Boas, E.: The Effect of Pyloric Obstruction in Relation to Gastric Tetany, Bull. Johns Hopkins Hosp. **31**:1-7, 1920.

10. McCann, W. S.: A Study of the Carbon Dioxide Combining Power of the Blood Plasma in Experimental Tetany, J. Biol. Chem. **35**:553-563, 1918. A note on the Use of Ammonium Chloride in Gastric Tetany, Proc. Soc. Exper. Biol. & Med. **19**:393-394, 1922.

the plasma and an increase of the alkaline reserve. They obtained similar nerve reactions following the intravenous administration of large quantities of carbonate or bicarbonate of soda, which indicates the importance of the disturbance of the acid-base equilibrium.

Hastings, Murray and Murray [11] confirmed the changes in carbon-dioxid combining power and chlorids of plasma in experimental pyloric closure. No significant changes were noted in the hydrogen-ion concentration of the serum, but sulphur and phosphorus were markedly increased.[12] Harrop [13] and Healy [14] described tetany in accidental sodium bicarbonate poisoning in cases without gastric lesions. Tileston and Comfort [15] have shown a marked increase of total nonprotein nitrogen and urea in the blood in cases of acute intestinal obstruction. They were not inclined to ascribe this to renal injury, but rather to increased tissue destruction, for two reasons; first, the retention of nitrogen disappeared following operative relief of the obstruction; second, the retention was associated with indicanuria. They admit that decreased elimination of nitrogen and loss of fluid may play a part.

Louria [16] and Rabinowitch [17] have reported similar increases in the nonprotein nitrogen of the blood in postoperative ileus, general peritonitis and acute pancreatitis. An analysis of these cases indicates that they differ from those included in our group. They are not of the tetany type, but include many varied pictures of the intra-abdominal infections. Necropsy studies in the cases of Louria and Rabinowitch did not reveal renal lesions, at least not the renal lesions appearing in our cases.

Cooke, Rodenbaugh and Whipple [18] verified in animal experiments the existence of an increased nonprotein nitrogen content in the blood,

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11. Hastings, A. B.; Murray, C. D., and Murray, H. A., Jr.: Certain Chemical Changes in the Blood After Pyloric Obstruction in Dogs, J. Biol. Chem. **46**:223-232, 1921.

12. Greenwald holds that in parathyroprival tetany phosphoric acid is retained and that the condition is not one of alkalosis but of acidosis. Greenwald, I., and Lewman, Gertrude: The Determination of the Titratable Alkali of the Blood, Jour. Biol. Chem. **54**:263-283, 1922.

13. Harrop, G. A., Jr.: The Production of Tetany by Intravenous Infusion of Sodium Bicarbonate, Bull. Johns Hopkins Hosp. **30**:62-63, 1919.

14. Healy, W. P.: Postoperative Tetany Due to Sodium Bicarbonate, Am. J. Obst. & Gynec. **2**:164-170, 1921.

15. Tileston, W., and Comfort, C. W., Jr.: The Total Nonprotein Nitrogen and the Urea of the Blood in Health and in Disease, as Estimated by Folin's Method, Arch. Int. Med. **14**:620-649 (Nov.) 1914.

16. Louria, H. W.: The Blood Urea Nitrogen in Acute Intestinal Obstruction, Arch. Int. Med. **27**:620-628, 1921.

17. Rabinowitch, I. M.: The Prognostic Value of the Study of the Blood Chemistry in the Acute Abdomen, Canad. M. A. J. **11**:163-166, 1921.

18. Cooke, J. V.; Rodenbaugh, F. H., and Whipple, G. H.: Intestinal Obstruction. VI. A Study of Non-Coagulable Nitrogen of the Blood, J. Exper. M. **23**:717-738, 1916.

and demonstrated similar increases after proteose injections. Histologically they were unable to find renal lesions. Subsequently, McQuarrie and Whipple,[19] in an experimental study of intestinal obstruction and proteose intoxication, proved conclusively that renal function was definitely impaired. They found a decreased elimination of phenolsulphonephthalein and chlorids in the urine with increased concentration of urea in the blood, and pointed out the possible clinical importance of these observations.

Hardt and Rivers[20] have reported an interesting and important group of cases in which, during the course of alkaline treatment for ulcer, toxic symptoms developed. Their cases exhibited albuminuria, cylindruria and a rise in the blood urea and in the alkaline reserve; there was also clinical evidence of renal insufficiency. In the two cases coming to necropsy, an acute exacerbation of chronic nephritis was found.

Tisdall's[21] observations indicate that the sodium-calcium relation is not disturbed in gastric tetany. These findings we are able to substantiate.

Credit for recognizing the clinical importance of the renal factor in the toxemia and death following gastro-enterostomy belongs to Tucker,[22] formerly of the Mayo Clinic, who reports eight cases from the Clinic in which uremia developed following gastro-enterostomy. He believed uremia to be the probable cause of death. In four of his cases, necropsy revealed the grafting of an acute process on a previously existing chronic nephritis. It is significant that in not a single instance did he find any local, organic lesion in the wall of the intestine adequate to explain the toxemia and death. From an experimental and clinical point of view, the following conclusions seem to be established:

1. Complete continued obstruction of the duodenum or upper jejunum causes a fatal toxemia.

2. The obstructed duodenal contents, when injected into animals, cause symptoms of intoxication similar to those obtaining in the obstructed animal.

3. Blood analysis shows (*a*) decreased plasma chlorids, (*b*) increased carbon dioxid combining power of the plasma, and (*c*) increased blood urea.

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19. McQuarrie, I., and Whipple, G. H.: I. Renal Function Influenced by Intestinal Obstruction, J. Exper. M. **29**:397-419, 1919. II. Renal Function Influenced by Proteose Intoxication, J. Exper. M. **29**:421-444, 1919.

20. Hardt, L. L., and Rivers, A. B.: Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer, Arch. Int. Med. **31**:171-180, 1923.

21. Tisdall, F. F.: The Influence of the Sodium Ion in the Production of Tetany, J. Biol. Chem. **54**:35-41. 1922.

22. Tucker, W. J.: Uremia Following Gastro-Enterostomy, Eight Cases, Wisconsin M. J. **20**:528-529, 1922.

4. There is no unanimity of opinion as to the nature of the toxic substances or as to the exact cause of death, but Whipple's and Dragstedt's work ascribing the toxemia to the formation of substances of a proteose nature produced in the duodenum is the most convincing evidence available, while Gerard's suggestion that histamin is responsible for the toxemia is worthy of consideration.

A Clinical Study of Duodenal Intoxication.—This report is concerned with the clinical, pathologic and biochemical studies in a series of eleven cases of duodenal toxemia; the patients are classified in two groups.

Group 1: The preoperative group, in which the obstruction followed an organic lesion involving the duodenum; five cases: Case 1, carcinoma of the middle portion of the duodenum; Case 2, duodenal ulcer with pyloric obstruction; Case 3, carcinoma of the stomach, involving the pylorus with obstruction; Case 4, chronic duodenal ulcer with stenosis, and Case 5, carcinoma of the pancreas, obstructing the lower third of the duodenum.

Group 2: The postoperative group, in which organic duodenal obstruction or functional stasis followed operation; six cases, considered in two groups: (*a*) acute duodenal obstruction in which symptoms appeared from five to eleven days following operation; Case 6, posterior gastro-enterostomy for duodenal ulcer followed in five days by obstructive toxemia. No anatomic explanation was found in the duodenum to account for the toxemia; Case 7, posterior gastro-enterostomy for saddle ulcer of the first and second portions of the duodenum (involving the pancreas), clinical evidences of obstruction appearing ten days later; Case 8, posterior gastro-enterostomy for duodenal ulcer 1.25 cm. below the pylorus. Mild obstructive symptoms were noted five days later. (*b*) Chronic duodenal obstruction in which symptoms appeared from six weeks to six months or more after operation on the stomach or duodenum: Case 9, gastrojejunal ulcer six years after a posterior gastro-enterostomy; Case 10, gastro-enterostomy for duodenal ulcer; there were chronic obstructive symptoms for five years; there was kinking of the jejunoduodenal juncture; Case 11, gastro-enterostomy for supposed duodenal ulcer; obstructive symptoms appeared six months later; there were adhesions and kinking of the proximal loop.

REPORT OF CASES

In the following case reports the degree of retention obstruction, casts etc., is represented by a figure on the basis of grades 1 to 4.

Case 1 (A333574).—Mr. W. R. T., aged 61, entered the Mayo Clinic on Sept. 11, 1920, complaining of epigastric distress of six months' duration, having begun as a dull, aching pain. The periods of remission from pain had not exceeded three days. The pain was exaggerated two or three hours after eating and was not relieved by food or alkalis. For the last two months the

patient had vomited at least once in twenty-four hours, and food retention of twelve hours had been noted. The weight loss of 25 pounds (11.33 kg.) had been progressive. Blood had not been noted in the vomitus or stools.

On examination, the patient appeared to be extremely sick; he was emaciated, weak, and had a dry skin. There was slight diffuse tenderness in the epigastrium. In the right hypochondrium an indefinite, sausage-shaped mass was palpable, movable and slightly tender. The edge of the liver was felt. The ophthalmoscopic examination was negative. The systolic blood pressure was 98, the diastolic, 80. Two months before, the readings had been 125 systolic and 75 diastolic. The gastric contents revealed total acidity, 26; free hydrochloric acid, 14; food remnants, 1; and sarcines, 1; the total amount of contents recovered being 700 c.c. Roentgenologic examination revealed retention 2 (on the basis of 1 to 4), but no lesion. With the exception of an occasional hyaline cast, no abnormalities were found in the urine. The blood contained: hemoglobin, 76 per cent. (Dare); erythrocytes, 4,720,000; and leukocytes, 7,200. The blood urea was 124 mg., and creatinin 23 mg. for each 100 c.c. The phenolsuphonephthalein (intravenously) excretion was 10 per cent.

A diagnosis was made of pyloric obstruction with chronic nephritis and marked renal insufficiency. In view of the serious condition of the patient, operation was not deemed advisable at the time and medical management was instituted, consisting of glucose and alkalis by rectum, limited liquids by mouth and gastric lavage twice daily. Alkalis were stopped when alkalosis was recognized. On September 24, after a motor meal, no retention was demonstrated. The condition of the patient remained constant until September 30, when he had a slight convulsion, characterized by generalized quivering. His pulse was feeble and he seemed much weaker. One-half hour later the patient vomited 600 c.c. of a thin, pea-soup fluid. He complained of tingling sensations in the face and hands; later in the day, the vomiting became almost continuous. His mental condition remained clear until October 2, when definite mental aberration was noted. An exploratory operation was performed and a gastro-enterostomy in an attempt to relieve the obstruction. A hard, firm mass was found 15 cm. below the pylorus involving the duodenum and the head of the pancreas. The proximal portion of the duodenum was dilated as was the stomach. Immediately following the operation the patient exhibited muscular twitchings; five cubic centimeters of 5 per cent. calcium chlorid solution were administered intravenously every six hours. On the second day his condition remained about the same, but toward evening he became unconscious and died the next day.

At necropsy the pancreas was found to be normal in size, and its duct was patent throughout. In the outer portion of the head, near the central portion of the duodenum, was a firm mass. The first portion of the duodenum was greatly distended. On opening it a hard, round, crater-like ulceration with thickened, indurated margins was found 1 cm. below the pylorus and 3 cm. above the ampulla of Vater. This mass was intimately adherent to the pancreas and continuous with the small pancreatic mass previously mentioned. The duodenal wall in this region was thickened and very firm in consistency. An opening was found in the greater curvature of the stomach 5 cm. proximal to the pylorus, which admitted three fingers and opened into the jejunum 5 cm. from the duodenojejunal juncture. There was no leakage at the suture line. The right and left kidneys weighed, respectively, 180 and 215 gm. The capsules stripped with ease and left a smooth, congested surface. On section, the organs were moderately congested throughout, and the markings of the cortex and column of Bertini were indistinct. The rays of the pyramids appeared as red lines and were fairly prominent. Scattered over the cortex of both kidneys were numerous, pin-point, whitish nodules. In the mucosa of the pelvis of the left kidney were a few tiny foci of hemorrhages. There were no abnormalities noted in the remainder of the genito-urinary tract. The heart weighed 350 gm. The myocardium was soft and flabby and had a slight brownish tinge. In the

coronary arteries, more especially in the left root of the aorta and the leaflet of the mitral valve, were numerous small patches of yellowish thickening. The lungs revealed small areas of bronchopneumonia.

The histologic examination of the heart muscle revealed areas of marked fragmentation. Sections of the lungs showed small areas of bronchopneumonia. The glomeruli of the kidney were lobulated and decreased in size. Small areas of lymphocytic infiltration were seen in the interstitial tissue. The tubules revealed degeneration in certain areas. There was slight increase in the interstitial tissue throughout the section (Fig. 1). The muscular and submucosal layer of the duodenum revealed infiltration by cells having a definite glandular arrangement. The cells were epithelial-like and were divided into small islands by bands of fibrous tissue.

The case was one of primary carcinoma of the duodenum causing obstruction and chronic distention of the first portion of the duodenum and stomach. There was marked evidence of renal insufficiency as

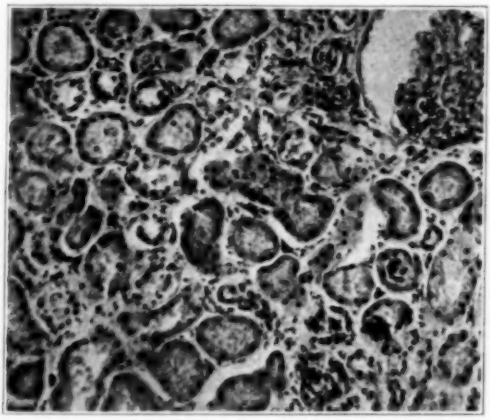

Fig. 1 (Case 1).—Section of kidney showing areas of tubular degeneration and calcareous deposits in the tubules (× 100).

shown by the urine and in the increase of blood urea and creatinin and the low excretion of phenolsulphonephthalein. The clinical picture was that of gastric tetany and uremia associated with a high grade alkalosis. Muscular twitchings, vomiting, mental aberration and asthenia with associated blood findings constitute a syndrome that cannot be differentiated from that of uremia. The necropsy findings of severe toxic nephritis bear out this assumption (Table 1).

Case 2. (A297046).—Mr. F. W. M., aged 52, came to the Clinic on Sept. 25, 1921, complaining of gastric distress of fifteen years' duration with remissions for periods as long as three years. The distress came on about two and one-half hours after meals, and was especially marked during the night. Relief was usually obtained by food and alkalis. Three years earlier the condition was diagnosed duodenal ulcer, and medical treatment was given. Albumin was

TABLE 1.—*Findings in Case 1*

Date	Blood: Hemoglobin (Dare) Percentage	Blood: Urea, Mg. for Each 100 C.c.	Blood: Creatinin, Mg. for Each 100 C.c.	Blood: Carbon Dioxid, Volume, Percentage	Blood: Uric Acid, Mg. for Each 100 C.c.	Urine: Albumin	Urine: Sediment	Urine: Phenolsulphonephthalein, Percentage	Blood Pressure: Systolic	Blood Pressure: Diastolic	Remarks
7/10/20	..	...	...	...	...	...	Hyaline casts 1	..	125	75	Before admission
9/13/20	76	...	...	...	...	...	Hyaline casts 1	10	98	80	
9/16/20	78	124	2.3	...	...	1	Hyaline casts 1	..	...	..	Continual vomiting
9/21/20	..	120	1.7	...	...	2	Hyaline casts 1	..	98	80	Continual vomiting
9/23/20	..	...	...	...	...	2	.....	No return	...	..	Continual vomiting
9/28/20	..	...	...	...	7.0	2	Hyaline casts 1	5	...	..	Continual vomiting
9/30/20	82	100	...	...	9.9	...	.....	..	98	80	Nervous manifestations of tetany
10/ 2/20	..	...	...	158	...	...	.....	..	...	..	Chvostek positive

TABLE 2.—*Chemical Studies of the Blood During Period of Duodenal Toxemia (Case 2)*

Date	Urine: Specific Gravity	Urine: Reaction	Urine: Albumin	Urine: Erythrocytes	Urine: Casts	Blood: Carbon Dioxid, Volume, Percentage	Blood: Creatinin, Mg. for Each 100 C.c.	Blood: Urea, Mg. for Each 100 C.c.	Blood: Plasma Chlorids, Mg.	Phenolsulphonephthalein Excretion, Percentage	Blood: Hemoglobin (Dare) Percentage	Blood: Erythrocytes	Blood: Leukocytes	Gastric Acids: Total	Gastric Acids: Free Hydrochloric	Blood Pressure: Systolic	Blood Pressure: Diastolic	Blood: Sodium, Mg. for Each 100 C.c.	Blood: Potassium, Mg. for Each 100 C.c.	Blood: Calcium, Mg. for Each 100 C.c.
9/26/21	1.014	Acid	1	2	2	..	4.3	225	...	..	73	4,500,000	7,400	74	54	124	98	...	.....	...
9/29/21	1.011	Alkaline	1	...	...	80	4.7	161	560	..	..	.....	.....	..	..	120	29	...	.....	....
10/ 1/21	1.013	Alkaline	...	...	...	82	...	170	...	..	..	.....	.....	..	..	133	87	325	22	....
10/ 4/21	.....	.....	...	...	...	80	5.0	214	500	..	77	4,030,000	6,200	54	40	...	..	...	.....	...
10/ 6/21	.....	.....	...	...	...	86	5.5	226	485	5	77	3,960,000	10,600	..	..	...	..	381	.....	13.3
10/ 8/21	1.009	Acid	1	...	1	78	4.5	226	520	..	..	.....	.....	..	..	...	..	...	.....	....
10/10/21	1.012	Acid	1	...	1	76	4.4	198	...	..	..	.....	.....	..	..	120	80	...	.....	....
10/12/21	1.013	Acid	1	...	1	58	4.4	160	600	10	..	.....	.....	..	..	...	..	...	.....	....
10/14/21	1.011	Acid	1	...	1	62	3.8	126	637	10	76	4,580,000	6,400	..	..	...	..	...	.....	....
10/17/21	1.011	Acid	1	...	1	59	3.5	105	615	..	..	.....	.....	..	..	130	40	...	.....	....
10/19/21	.....	.....	...	...	...	59	2.9	73	623	..	..	.....	.....	..	..	...	..	...	.....	....
10/21/21	.....	.....	...	...	...	56	2.6	43	660	..	70	3,900,000	6,600	..	..	...	..	...	.....	....
10/24/21	.....	.....	...	...	...	..	2.2	39	670	..	..	.....	.....	..	..	137	84	...	.....	....
10/27/21	1.011	Acid	1	...	...	..	2.3	42	635	..	68	3,700,000	5,600	..	..	...	..	...	.....	....
11/ 2/21	.....	.....	...	...	...	56	...	33	640	..	68	3,720,000	5,600	..	..	...	..	...	.....	....
11/ 8/21	1.010	Acid	1	...	...	..	2.1	30	645	15	66	3,480,000	7,200	..	..	...	..	...	.....	....
11/11/21	Gastro-enterostomy																			
11/23/21	1.015	Acid	1	...	..	50	2.7	36	635	20	..	.....	.....	..	..	...	..	...	.....	....
11/28/21	.....	.....	...	...	..	71	2.4	35	...	25	68	3,620,000	6,800	..	..	100	96	...	.....	....

found in the urine, but there was no other evidence of renal insufficiency. For one year there was freedom from gastric symptoms. The present attack had begun ten days before admission. Relief from pain had been obtained by an exclusive milk diet and large doses of alkalis. Three days later he had begun to vomit and this continued. The patient said that everything he ate "seemed to back up" on him.

In the course of the routine laboratory examination, a blood urea of 222 mg. for each 100 c.c. was found. The systolic blood pressure was 124 and the diastolic 98. A trace of albumin, hyaline and granular casts and occasional erythrocytes were found in the urine. Mild but distinct mental symptoms existed as evidenced by irritability and slight drowsiness. Because of the renal insufficiency, the patient was hospitalized for medical treatment preparatory to operation for duodenal ulcer. The treatment consisted of 1 liter of 5 per cent. glucose solution by rectum, 1 liter of milk by mouth and high carbohydrate and low protein diet. Dilute hydrochloric acid and calcium chlorid were given by mouth. No obstruction was demonstrable by barium or twelve-hour motor meals. Under this regimen, the patient improved rapidly (Table 2). No alkalis were administered. Following the improvement in the renal condition, the patient was allowed to return home for ten days before the anticipated operation.

The operation was performed on November 11, by W. J. Mayo. An ulcer covering three-fourths of the circumference of the duodenum was found extending up to and involving the pylorus. Obstruction 3 (on the basis of 1 to 4) was found. The tip of the finger could not be introduced into the pyloric canal. The appendix was removed. The gallbladder was adherent, but was not removed. The patient's convalescence was uneventful and renal functional studies showed a marked improvement. An examination was made eight months later, and slight impairment of renal function was still found. The phenolsulphonephthalein excretion in two hours was 40 per cent. and the blood urea 46 mg. for each 100 c.c. The systolic blood pressure was 155 and the diastolic 90. The urine contained albumin 2 and hyaline and granular casts 1. The patient's general physical condition was excellent.

A man, aged 52 years, with a long-standing history of duodenal ulcer, during an active stage of the ulcer, developed evidences of uremia. This was shown both in clinical and laboratory examinations. A definite alkalosis was present which may stand in causal relationship to excessive use of alkalis. The plasma chlorids were moderately reduced. No evidence of tetany was present. The important part played by the kidney in the clinical picture is demonstrated by markedly low excretion of phenolsulphonephthalein with a high urea and creatinin level in the blood, and evidence of renal irritation in the urine. The absence of elevated blood pressure allows us to classify this renal injury as a nephrosis. Operation resulted in a clinical cure with the disappearance of all symptoms and marked improvement in renal function.

CASE 3 (A367847).—Mr. H. L., aged 54, came to the Clinic on Aug. 9, 1921, because of stomach trouble of twenty years' duration, characterized by considerable nervous indigestion, with occasional vomiting of food at night. Five years before, the patient had had a gastric hemorrhage and melena. Following medical treatment he was in good health for two years. For the last two years he had been constipated, his abdomen was bloated, and he frequently vomited food eaten the day before. Vomiting was always preceded

by nausea. For the last three months the condition had been much worse. Only liquid foods had been eaten, but nausea and vomiting had occurred frequently.

Gastric analysis revealed total acidity 34 with free hydrochloric acid 16; a total of 1,024 c.c. of gastric contents were recovered. Roentgenograms of the stomach revealed dilatation 3, with a lesion at the outlet. The systolic blood pressure was 130, and the diastolic 98. The specific gravity of the urine was 1.026, albumin 1, and the sediment was negative. The blood contained: hemoglobin, 68 per cent. (Dare); erythrocytes 4,270,000 and leukocytes 4,600.

The patient was sent to the hospital for preoperative treatment. With daily gastric lavage, amounts were recovered varying from 500 to 1,500 c.c. of thin, greenish fluid. Liquids were forced and glucose given by rectum; the patient was kept on a liquid diet. Two attacks of tetany occurred while the patient was under medical care, the second consisting of a tetanic type of convulsion, lasting thirty minutes and followed by marked prostration. The patient's general condition was not good. The fourth day after his admission to the hospital the blood urea was 80 mg., the carbon dioxid 105 volumes per cent. On August 13, five days after admission, a posterior gastro-enterostomy was performed. A tumor of the pylorus, which seemed to be causing almost complete obstruction, was found. It was impossible to determine whether or not the tumor was malignant, but it seemed to be a polyp. The operation was regarded as an emergency procedure because of the gastric tetany and renal insufficiency. Following the operation the patient became excitable and mildly delirious. His respiration was increased to 36. Fluids were given subcutaneously and by proctoclysis. Nothing important was discovered on physical examination. The same evening gastric lavage produced 240 c.c. of dark fluid, after which the patient felt fairly well. August 17, the specific gravity of the urine was 1.021; it contained albumin 2; hyaline casts 1. The blood urea was 88 mg. for each 100 c.c.; the blood creatinin, 2.4 mg. Convalescence was uneventful. A second operation was performed on September 5, when a carcinoma of the posterior wall of the stomach just above the pylorus was removed with about one-third of the stomach. This growth had a crater, but was not adherent posteriorly to the pancreas. The pathologists reported carcinoma without glandular involvement. The patient was dismissed from observation eighteen days after operation, at which time the values for blood nitrogen were normal, but a constant trace of albumin was still found in the urine.

This patient presented a long-standing history of epigastric distress of an obstructive nature, which was not typical of duodenal ulcer. For the last three months, retention features had been present, which were verified by clinical and laboratory examinations. While under medical management gastric tetany with renal insufficiency became evident. Diagnosis of toxic nephritis was made and surgical relief was given by removal of neoplasm of the duodenum before the condition had progressed to the fatal stage.

Case 4 (A317395).—Mr. O. P., aged 27, came to the Clinic on May 27, 1920, complaining of having had pain in the stomach, attacks of abdominal pain, nausea, vomiting, dizziness, constipation and occasional severe attacks of jaundice for eight years. Tarry stools and hematemesis had also been noted. The attacks recurred every five to eight months. The pain reached its maximum three hours after eating and after midnight. It was not relieved by food or soda, but usually by vomiting. The patient had lost 20 pounds (9.07 kg.) in weight, was easily exhausted and had syncopal attacks. He had not had special nervous symptoms, with the exception of insomnia.

Examination was practically negative except for distant heart sounds and definitely infected tonsils. The systolic blood pressure was 100 and the diastolic, 90. The urine was negative. The blood contained: hemoglobin, 68 per cent. (Dare); erythrocytes, 4,050,000; leukocytes, 6,200. The gastric analysis revealed: total acidity 80 and free hydrochloric acid 60; the total of gastric content recovered was 3,615 c.c. Roentgenograms of the stomach revealed a perforating duodenal ulcer, with retention 3. The clinical diagnosis was chronic perforating duodenal ulcer with history of obstruction.

The patient's condition was considered grave, and he was referred to the hospital for preoperative medical treatment. Daily gastric lavage, fluids by rectum, liquid diet, and proctoclysis of sodium chlorid solution were given. Each lavage was followed by immediate relief; the amounts recovered averaged 300 to 1,000 c.c., and the fluid was of a thin, serous type. On the third day, the patient complained of numbness of the fingers and difficulty in speaking. The systolic blood pressure was 110 and the diastolic 80. Neurologic examination revealed positive Chvostek and Trousseau signs. A diagnosis of gastric tetany was made. Aphonia followed the passing of the stomach tube. Calcium chlorid was given intravenously.

Operation was performed on June 8. The first part of the duodenum was found to be definitely contracted. The stomach was dilated, 4. A posterior gastro-enterostomy was performed. The patient became delirious and required morphin. However, he soon improved, and his temperature and pulse were normal for several days. Sodium chlorid by proctoclysis was given, with small amounts of water by mouth. One thousand and fifty cubic centimeters of urine were passed during the second twenty-four hours. The patient vomited occasionally, was very restless and at times irrational. His condition remained fairly satisfactory until the seventh day after the operation, then pain developed in the abdomen and the temperature and pulse rate increased, with other evidences of peritonitis. He died the ninth day after the operation.

Necropsy revealed general serofibrinous purulent peritonitis; an old healed duodenal ulcer with stenosis of the pylorous, double empyema with terminal bronchopneumonia, acute diffuse nephritis and acute hypoplasia of the lymphoid tissues of the body.

Histologic examination of the kidneys revealed increased interstitial connective tissue, lymphocytic infiltration in the stroma of the cortex and medulla and numerous foci of calcium salts with mulberry-like form. The crystals filled more particularly the collecting tubules.

This patient, with a typical history and clinical findings of duodenal ulcer with obstruction, following the institution of medical treatment, developed symptoms of duodenal intoxication with gastric tetany. At operation stenosis of the duodenum was found, and gastro-enterostomy was performed for relief. Death from general peritonitis and double empyema occurred in seven days. Necropsy revealed acute diffuse nephritis. This case was one of the earliest in the series, and blood chemistry and renal function studies were not made.

Case 5. (A413425).—Mr. J. C. C., aged 38, came to the Clinic on Dec. 25, 1922, because of gastric trouble of nine months' duration. He had been jaundiced about seven months before, but did not have pain. A cholecystostomy had been performed, and the symptoms were relieved. In October, a second operation had been performed to close the biliary fistula and to explore the stomach because of obstructive symptoms. A large mass was found involving the pancreas, which was diagnosed malignant. In order to relieve the common-duct obstruction, a tube was placed with one end in the gallbladder, the other end in the jejunum and united extra-abdominally, and a gastro-

TABLE 3.—*Findings in Case 5.*

	Blood					Urine				Blood Pressure		
Date	Hemoglobin, Acid-Hematin, Percentage	Urea, Mg. for Each 100 C.c.	Carbon Dioxid, Volume, Percentage	Chlorids, Mg. for Each 100 C.c.	Sodium of Serum, Mg. for Each 100 C.c.	Albumin	Sediment	Total Nitrogen, Gm.	Phenolsulphonephthalein, Percentage Intravenously	Systolic	Diastolic	Remarks
12/26/22	..	88	...	...	...	...	.....	....	..	102	78	
12/27/22	86	..	101	375	...	2	Hyaline, granular	....	30	118	78	Gastric acids, total 40, free 0
12/29/22	90	62	150	425	...	1	Hyaline and granular casts	10.7	..	...	..	
12/31/22	90	..	112	450	348 337	1	0	....	..	...	..	Hydrogen-ion concentration of blood plasma, p_H 7.4; urine chlorids, 0.34 gm.
1/ 2/23	..	38	163	395	...	...	.....	....	..	120	80	Gastric acids, total 34, free 16
1/ 3/23	..	54	144	425	...	...	.....	....	..	...	..	Hydrogen-ion concentration of blood plasma, p_H7.2; of urine, p_H 7.2
1/ 4/23	..	..	133	450	...	3	Hyaline and granular casts	....	..	...	..	Sodium in urine, 278 mg. for each 100 C.c
1/10/23	80	..	126	600	...	...	.....	....	50	...	..	
1/12/23	..	..	114	670	...	...	.....	....	..	...	..	

enterostomy was performed. The patient did very well following the operation up to two weeks before coming to the Clinic, when he began to develop definite symptoms of pyloric obstruction.

Examination revealed emaciation and evidence of dehydration. There was no jaundice. A rubber tube about 15 cm. in length lay across the abdomen, one end apparently passing into the gallbladder and the other into the duodenum; bile was passing through the tube freely. A large mass could be

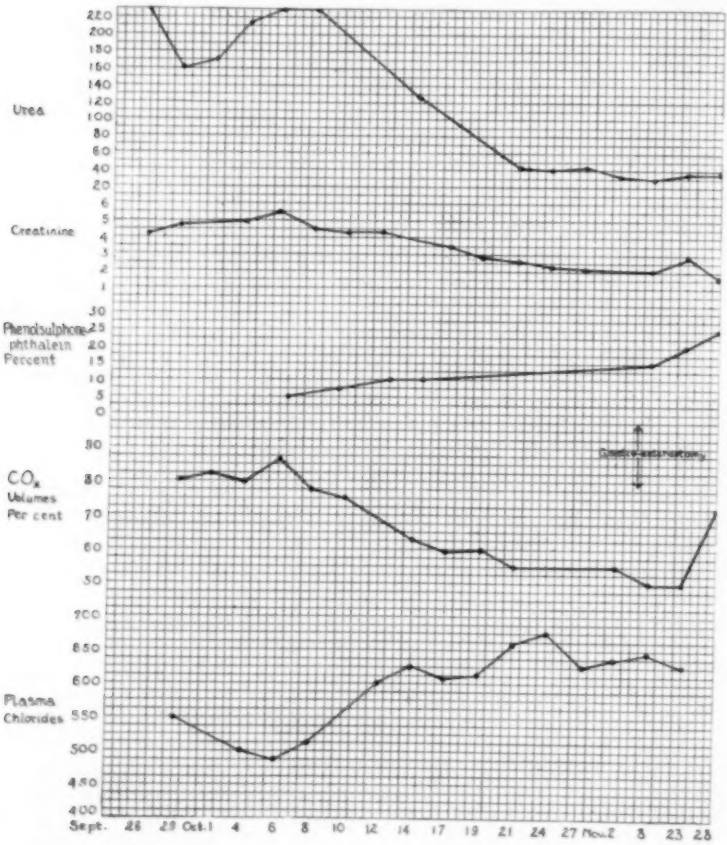
Urea
Creatinine
Phenolsulphonephthalein Percent
CO_2 Volumes Per cent
Plasma Chlorides
Sept. 26 29 Oct. 1 4 6 8 10 12 14 17 19 21 24 27 Nov. 2 8 23 28

Fig. 2 (Case 5).—Chart showing blood chemistry and renal function in duodenal toxemia.

palpated in the upper right quadrant which was apparently the liver or pancreas. The superficial abdominal veins were prominent. The urine was acid; it contained albumin 2 and a few pus cells. There were 15,000 leukocytes, 4,720,000 erythrocytes and 90 per cent. hemoglobin (Haldane-Palmer). The carbon-dioxid combining power of the blood was 101.

The patient was hospitalized for treatment on December 26. The first twenty-four hours he vomited about 800 c.c. of a watery, faint yellow fluid, with

a total acidity of 36 and a free acidity of 17. In thirty-six hours, the patient became drowsy and shortly afterward had a convulsion which was characterized by clenching of the hands, twitching of the facial muscles and clonic contractions of the whole musculature. This was followed by coma. The pulse was very weak, respirations were shallow, but the color remained good. Three more attacks occurred during the next twenty-four hours (Fig. 2). One thousand cubic centimeters of sodium chlorid solution were given subcutaneously and 500 c.c. of glucose solution by rectum; this did not control the convulsion. Eight hundred cubic centimeters of Ringer's solution containing an additional gram of calcium chlorid were given intravenously followed by a solution of sodium chlorid and glucose by rectum. In eight hours there was definite improvement, the patient was more rational and he had no more convulsions,

TABLE 4.—*Nitrogen Partition of Blood in Case 5* *

Date		Mg. for Each 100 C.c.	Percentage of Nonprotein Nitrogen
12/27/22	Total nonprotein nitrogen	75.0	100.0
	Urea nitrogen	49.0	66.0
	Creatinin nitrogen	0.89	1.6
	Uric acid nitrogen	2.46	3.3
	Amino nitrogen	7.20	9.6
	Rest nitrogen	15.25	20.5

Nitrogen Partition of Urine

		Gm.	Percentage
12/27/22	Total nitrogen	16.0	100.0
	Urea nitrogen	12.50	78.0
	Creatinin nitrogen	0.50	3.1
	Uric acid nitrogen	0.33	2.0
	Ammonia nitrogen	0.585	3.6
	Amino nitrogen	0.165	1.0
	Rest nitrogen	2.0	12.5

* The nitrogen partitions in this case were made by Dr. C. H. Green.

TABLE 5.—*Hydremia and Blood Volume Studies (Case 5)*

Date	12/31/22	1/10/23
Water content of whole blood, percentage	82.5	83.2
Water plasma, percentage	94.3	94.2
Hematocrit values—Erythrocytes, percentage	30.0	34.0
Plasma, percentage	70.0	66.0
Total plasma volume, c.c.	2962	2857
Plasma, c.c. for each kilogram	54	57
Total blood volume, c.c.	4231	4328
Blood, c.c. for each kilogram	78	86
Haldane-Palmer hemoglobin, percentage	90.0	80.0

although he was restless and talked irrationally at times. He continued to improve, and 20 gm. of sodium chlorid and 600 c.c. of water were passed daily through the tube into the duodenum, with feedings of lactose, glucose and peptonized milk. His condition continued to improve. There was a decrease of blood urea and increasing phenolsulphonephthalein excretion. Obstructive symptoms were constant and larger amounts were recovered than given. On January 12, an exploratory operation was performed. General carcinomatosis was found, which involved the liver, pancreas and peritoneum. In the stomach and jejunum was a large mass of carcinomatous tissue. The patient died from exhaustion the third day after operation (Tables 3, 4 and 5).

Necropsy revealed carcinoma of the pancreas with peritoneal carcinomatosis and metastasis to the liver, obstruction of papilla of Vater and duodenal lumen with dilatation of the common duct, ancient gastro-enterostomy, recent enterostomy, ancient cholecystostomy, hypostatic edema and congestion of the lungs

and acute diffuse nephritis. The left kidney weighed 180 gm. and the right 205 gm.; the right was extremely congested and edematous; the cortex was thickened; the markings were indistinct; the left kidney did not present gross abnormalities.

This patient [23] had carcinoma of the pancreas obstructing the lower third of the duodenum. Obstructive symptoms were present for three months. The first examination revealed the usual chemical and clinical evidence of duodenal toxemia with gastric tetany. Renal insufficiency was demonstrated by albuminuria, azotemia and diminished phenolsulphonephthalein excretion. The total nitrogen excretion in the urine revealed a normal amount for the twenty-four hours. The excretion of this quantity of nitrogen on a low protein diet and in the presence of a definite renal injury would seem to indicate an abnormally high degree of protein destruction. No leucin or tyrosin crystals were found. No evidence of sodium poisoning was obtained as normal values were found in the blood. No significant change was noted in the hydrogen-ion concentration of the blood. The shock features were not pronounced. The total blood and plasma volumes were within normal limits. Following treatment the total blood volume was not definitely increased. It is interesting to note the improvement in renal function, following the control of the toxemia by treatment. Necropsy revealed malignant obstruction of the duodenum and acute diffuse nephritis.

Case 6 (A383808).—Mr. A. F. H., aged 32, came to the Clinic on Feb. 10, 1922, because of epigastric distress of twelve years' duration. An appendectomy had been performed one year before, without relief. The patient had had periods of distress once or twice yearly, which continued for from two to four months. The pain usually reached its height about two hours after eating. Relief was obtained by food and soda, and partial relief by a diet of milk and cereal. Occasionally he vomited food eaten twelve hours before.

The patient was well developed, of good color, and weighed 150 pounds (68 kg.). The systolic blood pressure was 120 and the diastolic 70. The blood contained: hemoglobin (Dare), 79 per cent.; erythrocytes, 4,800,000; and leukocytes, 4,460. Urinalysis was negative. Gastric analysis showed a total acidity of 70 and free hydrochloric acid of 50; a total of 170 c.c. of gastric content was recovered. The blood urea amounted to 33 mg. for each 100 c.c. The roentgenologist reported "duodenal ulcer without obstruction." The diagnosis of duodenal ulcer was clear cut, and surgical treatment was advised.

Operation was performed on February 20. An ulcer with a large amount of induration, due to inflammatory reaction, was found below the pylorous. There was obstruction, and the stomach was dilated 2. A posterior gastroenterostomy was performed. The convalescence was uneventful until the fifth day, when the patient complained of a sensation of fulness in the abdomen with distress and discomfort. Relief followed the vomiting of 300 c.c. of bile-stained fluid. On February 26, by gastric lavage, 500 c.c. of dark green fluid were recovered. On February 27, lavage was attempted, but no fluid was recovered. Six hours later 800 c.c. of fluid were recovered and four hours later 600 c.c.

23. Dr. C. F. Dixon will make a separate report of this case showing the effects of different forms of treatment on the carbon-dioxid combining capacity of the blood and chlorid content of the plasma.

On February 28, the patient vomited 350 c.c. of greenish fluid and later with gastric lavage 800 c.c. of fluid were recovered, after which the patient made fair progress for four days. On March 3, the patient complained of epigastric distress and lavage recovered a large amount of thin, greenish fluid. The patient seemed definitely weaker, somewhat dull mentally, and the pulse and respiration were slow. Trousseau and Chvostek reactions were not obtained.

TABLE 6.—*Findings in Case 6*

	Blood Chemistry	
3/2/22	Urea, mg. for each 100 c.c.	192
	Carbon dioxid, volumes percentage	84
	Plasma chlorids, mg. for each 100 c.c.	320
	Creatinin, mg. for each 100 c.c.	3.7
	Total nonprotein nitrogen, mg.	147
	Sodium, mg. for each 100 c.c.	412
	Potassium, mg. for each 100 c.c.	30.6
	Hydremia Studies	
	Whole blood viscosity	7.2
	Specific gravity, whole blood	1.070
	Palmer-Haldane hemoglobin, percentage	116
	Water content of whole blood, percentage	78.2
	Specific gravity of the plasma	1.035
	Water plasma, percentage	92.8
	Hematocrit values—Erythrocytes, percentage	46.2
	Plasma, percentage	53.8
	Total nitrogen, mg.	0.909

		Nitrogen Content in Gastric Secretion, Mg. for Each 100 C.c.			
	Reaction	Ammonia Nitrogen	Combined Urea and Ammonia Nitrogen	Urea Nitrogen	Estimated* Urea
3/2/22	Markedly alkaline	90	90	0	192.6

* Obtained by assuming the free ammonia to be derived in toto from urea. Therefore the combined urea and ammonia nitrogen is the correct index for estimating the urea, not the urea nitrogen alone.

TABLE 7.—*Chemical Data of Postmortem Fluids and Tissues (Case 6)*

Fluids	
Blood urea, mg. for each 100 c.c.	143*
Blood plasma chlorids, mg. for each 100 c.c.	253
Spinal fluid urea, mg. for each 100 c.c.	296

	Tissue, Mg. for Each 100 C.c.			
	Ammonia Nitrogen	Combined Urea and Ammonia Nitrogen	Urea Nitrogen	Estimated Urea
Kidney	29.8	134.5	104.6	387.0
Stomach	75.0	268.9	194.0	575.0
Liver	24.3	188.0	163.7	402.3

	Estimation of Chlorids			
	Wet Weight, Gm.	Dry Weight, Gm.	Water, Gm.	Sodium Chlorid, Mg. for Each 100 Gm. Fresh Tissue
Kidney	5	0.775	4.225	400
Stomach	5	0.850	4.150	200
Liver	5	1.352	3.648	400

* Probably low.

At times the hands assumed the position characteristic of tetany. The systolic blood pressure was 80 and the diastolic 55. The extremities were cold, and there was some cyanosis of the hands, with a florid red color of the cheeks and ears; the skin was dry, and the features were sunken. The temperature and pulse were normal. At 11 a. m., the patient developed symptoms of tetany, slight tonic convulsions, typical position of the hands and partial unconsciousness. He died in complete coma the following morning (Tables 6 and 7).

Necropsy revealed diverticulum of the duodenum, possibly the result of an ulcer, marked dilatation of the stomach, toxic nephritis with terminal bronchopneumonia, and arteriosclerosis, 1. The right kidney weighed 135 gm. and the left 130 gm. The capsules stripped readily, leaving a smooth surface. The cortices and medulla were clearly demarcated, and the cortical markings were fairly regular and distinct. There was slight bulging of the columns of Bertini. The stomach contained about 1,000 c.c. of sour, milky fluid. Grossly, the mucosa was normal. About 3 cm. beyond the pylorus on the posterior superior surface was an outpouching of the duodenum about 3 cm. in diameter and 3 cm deep. The remainder of the duodenum and its contents were intact. The upper 25 cm. of the jejunum was injected.

Histologic examination revealed many small areas of bronchopneumonia. Lymph nodules were fairly prominent and relatively numerous in the spleen. Marked calcium deposit was present in the cortex of the kidneys, and brownish pigment in the cells of the collecting tubules; the tubules contained many casts in the lumina. The blood vessels were congested. Granular changes were noted in the tubular epithelium. Sudan III sections demonstrated that the epithelium of the convoluted and collecting tubules contained a large amount of fat.

On this patient, who had a well defined clinical history of duodenal ulcer, a posterior gastro-enterostomy was performed. Five days later, he developed intermittent obstructive symptoms. Gastric tetany developed, with symptoms of duodenal intoxication, ending in death. The chemical studies of the blood revealed the characteristic changes, that is, lowering of plasma chlorids and increases of the level of the non-protein nitrogen ,urea, creatinin and increased carbon dioxid carrying capacity; also evidence of blood concentration.

Case 7 (A382714).—Mr. A. L. B., aged 41, came to the Clinic because of epigastric pain of twenty years' duration, occurring two to three hours after meals, and relieved by food and alkali. The attacks recurred once or twice annually and lasted three or four months. A remission lasting three years occurred in one instance. A history of obstruction could not be elicited.

The hemoglobin was 75 per cent. (Dare); the systolic blood pressure was 110 and the diastolic 70. The gastric contents showed a total acidity of 32 and free hydrochloric acid 22. Roentgenograms revealed a duodenal ulcer without obstruction.

Surgical interference was advised on account of the chronicity of the lesion and operation performed. A saddle ulcer, involving the upper margin of the duodenum and adherent to the pancreas, was found. A posterior gastro-enterostomy was performed. The postoperative convalescence was uneventful, and the patient was dismissed on the ninth day to the convalescence hospital. On the tenth day, he complained of epigastric distress. He vomited 240 c.c. of greenish fluid and was relieved. The stomach tube was passed daily and varying amounts of thin, greenish, fluid were recovered. On March 16, tonic contractions of the arms were present. The patient complained of severe pains in the arms and in the epigastrium. Two days later he became weaker and frequently vomited large amounts of the green, thin fluid. The hands assumed the position characteristic of tetany, and there was one generalized convulsion. The face, ears and hands were florid red. The vomiting continued, and there was marked puckering of the mouth. The patient was very restless; his extremities moved continuously. The following day the condition remained the same, with symptoms of tetany becoming more marked. An abdominal exploration was performed under local anesthesia, but obstruction was not found. Gastrostomy was then performed. From the onset, medical treatment including frequent

gastric lavage, 10 c.c. of dilute hydrochloric acid by rectum twice daily, calcium chlorid, 10 c.c. of 10 per cent. solution twice daily, and fluids by rectum, 5 per cent. glucose solution, were given. The condition continued to grow worse, and the patient died thirteen days after the onset of the obstructive symptoms (Table 8).

Necropsy revealed perforating chronic duodenal ulcer, posterior gastro-enterostomy and gastrostomy, acute toxic nephritis, terminal edema of the lungs with bronchopneumonia, arteriosclerosis and congestion of the brain. The short-loop gastro-enterostomy did not reveal leakage. The stoma admitted two fingers. The stomach was dilated, 2. In the posterior portion of the duodenum 5 cm. below the pylorus, there was a small, partially healed ulcer, moderately indurated and firmly adherent to the pancreas, measuring 1 by 0.8 cm. The suprarenals and pancreas were normal, grossly. The kidneys weighed 175 gm. each; the capsules stripped easily; the cortex was thickened and regular; the striae were indistinct.

TABLE 8.—*Chemical Studies of the Blood, Gastric Contents, Urine and Spinal Fluid in Case 7*

	Blood						Gastric Contents		
Date	Urea, Mg. for Each 100 C.c.	Creatinin, Mg. for Each 100 C.c.	Chlorids, Mg. for Each 100 C.c.	Carbon Dioxid, Volume Percentage	Sodium, Mg. for Each 100 C.c.	Potassium, Mg. for Each 100 C.c.	Sodium, Mg. for Each 100 C.c.	Potassium, Mg. for Each 100 C.c.	Urine Chlorids, Gm. for Each Liter
2/17/22	117	...	353	118	...	18.46	413	24	0.4*
2/20/22	235	...	445	125	306	15.9	.....	....	0.3*
2/22/22	Gastrostomy								
2/24/22	192	6	653	94	351	14.9 15.19	.....	....	0.2
2/24/22	Palmer hemoglobin 119								
2/27/22	Spinal fluid after death showed sodium, 405 mg. for each 100 c.c. and potassium 12 mg. for each 100 c.c.								

* Acid.

TABLE 9.—*Chlorids in Necropsy Tissues*

Tissue	Wet Weight, Gm.	Dry Weight, Gm.	Water Extract, Gm.	Chlorids, Wet, Mg. for Each 100 Gm. Fresh Tissue
Rectus muscle	5	1.3	3.7	120
Liver.....	5	1.25	3.75	256
Kidney.....	5	....	....	294
Brain.....	5	1.13	3.87	180
Lung.....	5	0.92	4.08	320
Heart.....	5	2.25	2.75	...

There was an occasional sclerosed glomerulus in the kidneys, with atrophy of corresponding tubules and lymphocytic infiltration. Some of the remaining glomeruli were lobulated, and slight interstitial fibrosis was present. The tubules showed acute changes. The tubular epithelium was swollen, granular and extensively disintegrated. The nuclei were pyknotic or had disappeared. In many tubules the epithelium had disintegrated entirely. Many of the necrotic cells showed extensive deposits of calcium salts. The lumen of the tubule contained disintegrated cells, coagulated fluid and many casts. The condition was diagnosed as acute toxic nephritis by Dr. Robertson (Fig 3). There was adipose replacement of the parathyroids (Table 9).

This patient had a typical history and roentgenologic findings of duodenal ulcer without obstruction. The operation revealed a large, adherent duodenal ulcer. A gastro-enterostomy was performed. Ten

days after operation, signs of duodenal obstruction with symptoms of gastric tetany developed. Exploration of the abdomen did not reveal the cause for the symptoms. The laboratory examinations gave evidence of marked renal insufficiency. The blood and urine chlorids were low, but following a relief drainage operation on the stomach the plasma chlorids returned to normal. An alkalosis was present. Normal values were obtained for sodium and potassium. The necropsy tissues showed chlorid depletion. The death in this case we believe can be explained on the basis of renal insufficiency, the duodenal stasis providing the toxic agent responsible for the injury. Necropsy demonstrated the existence of a severe toxic nephritis.

Case 8 (A108879).—Mr. A. P., aged 33, came to the Clinic on May 27, 1920, complaining of having had gastric distress with marked periodicity for

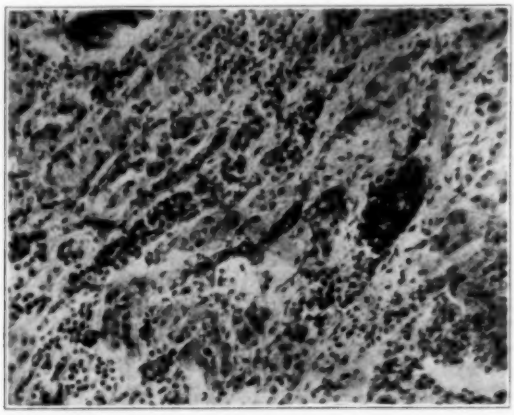

Fig. 3 (Case 7).—Section of kidney showing areas of tubular degeneration and calcareous deposits in the tubules (× 100).

ten years. The clinical history was typical of duodenal ulcer, with pain coming on about two hours after eating, worse at night and relieved by alkalis and food. He had been examined in the Clinic in 1914, and a diagnosis of duodenal ulcer made, but operation was refused. The patient was again admitted to the Clinic on Jan. 28, 1922.

Examination of the urine was negative. The blood contained 73 per cent. (Dare) of hemoglobin and 4,150,000 erythrocytes. Gastric analysis revealed a total acidity of 32 and free hydrochloric acid, 20; the total amount recovered was 175 c.c. The systolic blood pressure was 130 and the diastolic 80. Roentgenograms revealed duodenal ulcer without retention.

Operation was performed on Feb. 3, 1922. A duodenal ulcer 2 cm. in diameter was found within 1 cm. below the pyloric ring, but without obstruction. A posterior gastro-enterostomy was performed. The patient did very well until the fifth day, when he vomited 140 c.c. of bile-stained fluid. The tube recovered 600 c.c. of thin, greenish fluid. The temperature and pulse were normal. On the eighth day, 1,700 c.c. of thin, greenish fluid were vomited.

with relief of the distention distress. The patient continued in fairly good condition until the fifteenth day, when he was seized with a knife-like pain in the left axillary region which was aggravated by breathing, "catching his breath." Examination of the chest was negative. The temperature and pulse were normal. The leukocyte count was 9,100. On February 19, a similar attack of pain occurred, which was referred more to the epigastric region. The pulse rate was 120, and slight cyanosis was noted on the lips and tongue. Two thousand, five hundred cubic centimeters of gastric content were withdrawn, with relief from the pain. On February 20, 900 c.c. of fluid were withdrawn by gastric lavage. The respiration was 24, the pulse 88. The hemoglobin content was 80 per cent. (Dare); erythrocytes, 4,970,000. Chvostek and Trousseau signs were negative. On February 21, the patient was in fair condition; respiration was 30, there was slight hyperpnea; the face, ears and hands were strikingly florid. Lavage was continued every four hours. Dilute hydrochloric acid was given by mouth, 30 minims every four hours, and calcium chlorid was administered by rectum, 10 c.c. of a 10 per cent. solution twice daily. The urine showed a moderate trace of albumin, hyaline casts and erythrocytes. The patient's condition continued to improve, and no further retention was demonstrated by means of the gastric tube (Table 10).

TABLE 10.—*Chemical Studies (Case 8)*

	Blood			Gastric Contents			Urine		
Date	Urea, Mg. for Each 100 C.c.	Plasma Chlorids, Mg. for Each 100 C.c.	Carbon Dioxid, Volume Per-centage	Sodium, Mg. for Each 100 C.c.	Potas-sium, Mg. for Each 100 C.c.	Chlorids, Mg. for Each 100 C.c.	Potas-sium, Mg. for Each 100 C.c.	Chlorids, Mg. for Each 100 C.c.	Hemo-globin, Palmer-Haldane, Per-centage
2/20/22	30	450	92	...	..	...	..	..	...
2/21/22	31	428	93	355	19	...	..	..	...
2/23/22	17	455	98	...	..	...	..	..	116
2/24/22	...	...	..	...	..	439	64	80	...
3/ 1/22	20	610	68	...	..	...	..	..	...

Intermittent Obstruction as Shown by Amounts of Gastric Contents in Vomitus and Lavage

	February 11	February 14	February 19	February 20	February 24
	240 C.c.	1,700 C.c.	1,600 C.c.	180 C.c.	100 C.c.
	600 C.c.	150 C.c.	.....	2,500 C.c.	900 C.c.
	.....	.....	.....	300 C.c.	.....
Total	840 C.c.	1,850 C.c.	1,600 C.c.	2,980 C.c.	1,000 C.c.

This patient had duodenal ulcer without obstruction. Five days following gastro-enterostomy he developed signs of intermittent obstruction. Early signs of gastric tetany were present. There was a definite increase of carbon-dioxid combining power of the blood and a moderate decrease of plasma chlorids. The condition was relieved before severe renal injury resulted. No urea retention was present. The urine showed evidence of renal irritation. Unfortunately no estimation of the phenolsulphonephthalein excretion was made.

CASE 9 (A91674).—Mr. T. D., aged 28, came to the Clinic on Sept. 9, 1913, complaining of atypical symptoms of gastric ulcer, consisting of occasional vomiting of sour, thick material, bloating and continual epigastric distress. There was no definite food relief, but the pain was most severe from two to three hours after meals. He had had one attack of hematemesis. A roentgen-ray examination revealed obstruction of the pylorus and ulcer of the duodenum.

Examination of the urine was negative. The gastric contents after a test meal revealed a total acidity of 70 and free hydrochloric acid, 66.

On Sept. 17, 1913, a posterior gastro-enterostomy and an appendectomy were performed. Recovery was uneventful. The patient was again examined in the Clinic on March 20, 1919. He had felt fairly well after the operation, but he still had some gastric distress on overeating, indefinite bloating and a "tired feeling" in the stomach. He belched sour material, but he did not vomit. He said he thought his stomach was "closing up." Physical examination showed nothing of importance. The systolic blood pressure was 120, and the diastolic 70. Roentgenograms of the stomach revealed a gastrojejunal ulcer. Urinalysis was negative. A gastric test meal gave a total acidity of 30 and free hydrochloric acid, 20. The surgeons advised against operation because symptoms did not warrant it.

On May 17, 1919, the patient returned the third time because of more marked bloating, nausea and vomiting of green, watery fluid. He had lost 17 pounds (7.7 kg.) in weight in six months. The urine showed a specific gravity of 1.020 with a trace of albumin. Three days later albumin 2 and hyalin casts 3 were noted. Roentgenologic examination revealed a gastrojejunal ulcer with retention 1.

At operation on June 6, a gastrojejunal ulcer was found and excised. Until the seventh day the patient convalesced uneventfully, then he developed mild

TABLE 11.—*Findings in Case 9*

	Urine			Blood				
Date	Specific Gravity	Albumin	Casts	Hemoglobin, Percentage	Erythrocytes	Leukocytes	Urea, Mg. for Each 100 C.c.	Remarks
3/20/19	1.014	...	.....	76	.....	.....	...	
5/27/19	1.020	1	.....	..	.....	.....	...	
5/30/19	1.010	2	3 hyaline	..	.....	.....	...	Operated 6/4/19
6/11/19	1.025	3	3 hyaline 1 granular	87	5,440,000	12,900	120	Vomiting, marked fluid loss; signs of tetany
6/17/19	1.012	2	2 hyaline 1 granular	..	.....	.....	...	
6/23/19	.....	...	.....	..	.....	.....	101	
10/14/19	1.026	1	.....	80	.....	.....	...	General condition good; slight pain in arms and legs

obstructive symptoms. He complained of stiffness in the hands and feet. His face and mouth felt numb, his legs were cramped and his toes became flexed; he had pain in the side and back. Gastric lavage was given every six hours, the amounts of thin green fluid recovered averaging about 1,000 c.c. Proctoclysis, 10 c.c. of 5 per cent. solution of glucose in 240 c.c. of sodium chlorid solution and sodium bicarbonate were given. The patient was having definite spasms of tetany, the hands assuming the typical position. His general condition was not alarming. On June 13, gastric lavage returned clear. Ten hours later 150 c.c. of greenish fluid were recovered. The specific gravity of the urine was 1.012, the albumin was 2 and the hyalin casts 2. The urea content of the blood was 120 mg. for each 100 c.c. The hemoglobin content (Dare) was 87 per cent., the erythrocytes 5,440,000 and leukocytes 12,900, polymorphonuclear neutrophils 78.5 per cent. and small lymphocytes 21.5 per cent. On June 14, the patient complained of numbness in the hands and feet at the time of the lavage and said he would have a spasm if this were continued. On June 23, the blood urea was 101 mg. for each 100 c.c. Treatment was continued. On July 2, the condition cleared up entirely and at the last report the urine showed a faint trace of albumin. After the patient recovered he said that for the past ten or twelve years he had had periods of gastric distress associated with numbness, quivering of the lips and twitching of the abdominal muscles (Table 11).

A gastro-enterostomy was performed for duodenal ulcer. Progressive gastric symptoms with evidence of intermittent pyloric obstruction developed. Six years later a second operation revealed a gastrojejunal ulcer which was excised. Obstructive symptoms with gastric tetany developed after operation with clinical and laboratory signs of renal injury. The patient recovered. Subsequent reports have shown complete subsidence of renal damage.

CASE 10 (A369991).—Mr. T. R., aged 45, came to the Clinic on Aug. 26, 1921, because of "rheumatic pains" in the legs. A gastro-enterostomy had been performed elsewhere five years before, because of vague epigastric distress. Since then the patient had had intermittent epigastric distress, with vomiting and upper abdominal distention. For the last five months he had noted numbness, aching and cold sensations in the feet, and slight tingling in the fingers. He had lost 15 pounds (6.8 kg.) in weight.

The fractional gastric analysis showed achlorhydria, the total amount recovered being 435 c.c. The urine contained a trace of albumin. The hemoglobin content was 73 per cent. (Dare), and there were 4,190,000 erythrocytes. The

TABLE 12.—*Findings in Case 10*

	Blood								
Date	Urea, Mg. for Each 100 C.c.	Carbon Dioxid, Volume Percentage	Plasma Chlorids, Mg. for Each 100 C.c.	Sodium, Mg. for Each 100 C.c.	Potassium, Mg. for Each 100 C.c.	Calcium, Mg. for Each 100 C.c.	Gastric Chlorids, Mg. for Each 100 C.c.	Urine
9/ 3/21	255	98	285	...	.....	...	.....	.....
9/14/21	264	92	240	..	.....	..	.....	.....
9/15/21	260	88	290	361	4	7.2	.....	Acid
9/16/21	268	96	293	369	4	...	.....	.....
9/17/21	403	72	370	...	.....	...	369	0.12 gm. chlorid

roentgen ray revealed retention 3. A diagnosis was made of chronic pyloric obstruction with possible gastric tetany.

The patient was hospitalized for preoperative treatment consisting of gastric lavage and the forcing of fluids. The amount of gastric contents obtained by lavage ranged from 500 to 1,000 c.c. The night preceding the date set for operation the patient became unconscious and had convulsive twitchings. These symptoms became more severe and convulsions and mania developed. The hands assumed the tetany position. Chvostek and Trousseau's signs were positive. The treatment consisted of frequent gastric lavage with recovery of large amounts of contents. Calcium chlorid was given intravenously. On the sixth day, a left parotitis developed. The patient's condition became gradually worse and a shocklike state supervened, evidenced by low blood pressure, and red face and ears, suggesting dehydration. Weakness increased, and the patient died in coma (Table 12).

Necropsy revealed: ancient gastroduodenostomy with obstruction and permanent dilatation of the stomach and duodenum, bilateral coalescing bronchopneumonia, toxic nephritis, chronic right seminal vesiculitis, ancient tuberculosis of the right lung, and slight arteriosclerosis of the aorta.

The mucosa of the duodenum was deeply congested and almost gangrenous. No evidence of ulceration in the stomach was found, and the duodenum was widely patent. The left and right kidneys weighed 210 and 185 gm., respectively. The capsules stripped, leaving a smooth surface. The surfaces appeared moist. The cortical markings were indistinct. The glomeruli were visible as yellowish points.

Histologic examination revealed many casts in the tubules of the kidneys, foci of calcareous deposit and many foci of lymphocytic infiltration. Several epithelial crescents were seen in the glomerular cavity. The stroma was edematous (Table 13).

This patient had had a gastro-enterostomy performed elsewhere five years before. Symptoms developed resembling those of gastric tetany. The gastric symptoms were not marked at the time of examination. The clinical condition proceeded to that known as "duodenal intoxication." The tetany features of the case were marked. Later symptoms suggestive of uremia developed, associated with laboratory evidence of marked renal insufficiency. The necropsy examination confirmed the diagnosis of toxic nephritis.

Case 11 (A353616).—Mrs. T. B., aged 31, came to the Clinic on March 28, 1921, complaining of persistent loss of weight and strength. She had had periodic attacks of migraine. A gastro-enterostomy had been performed elsewhere in September, 1920, on the roentgenologic evidence of ulcer. Clinical evidence was lacking. For the first five days after the operation, the patient vomited large amounts of greenish, watery gastric contents. Following lavage the patient was free from gastric distress until three months later when

Table 13.—*Determination of Chlorids in Necropsy Tissues (Case 10)*

	Mg. for Each 100 Gm. Fresh Tissue
Brain	220
Wall of stomach	216
Liver	172
Muscle	80*
Kidney	208

* Probably low, difficult to extract.

obstructive symptoms, severe gas pains, nausea, marked loss of weight and strength, and frequent vomiting appeared almost daily.

The patient was emaciated and had a ventral hernia at the site of the operative scar. Her weight was 85 pounds (38.5 kg.). The systolic blood pressure was 85. Urinalysis showed specific gravity of 1.016, albumin 2 and an occasional hyaline cast. Examination of the blood revealed: hemoglobin, 80 per cent. (Dare); erythrocytes, 5,120,000; and leukocytes, 7,600. Roentgenograms of the stomach disclosed a large stomach with retention 2. A gastric meal showed a total acidity of 14 with free hydrochloric acid 8; 460 c.c. of contents were recovered.

The patient was hospitalized for preoperative treatment. Following gastric lavage and proctoclysis the vomiting was controlled and she gained 6 pounds (2.7 kg.) in weight. The stomach tube recovered 650 c.c. with some food remnants but no bile. The patient complained of numbness and twitching sensations in the hands and feet, particularly during the gastric tests. This was relieved by the aspiration of large amounts of the gastric contents. One definite attack of gastric tetany occurred with characteristic position of the hands, and thickness of speech. The Chvostek and Trousseau signs were present. The stomach was definitely distended, and 1,000 c.c. of greenish fluid were withdrawn, after which there was marked relief of the symptoms. The carbon dioxid combining power was 110. Operation was performed on April 26. The pylorus was opened, but there was no evidence of previous ulcer of the stomach or duodenum. The stoma was large, admitting three fingers.

Extensive adhesions had produced kinking of the proximal loop, and the bowel was twisted and turned to the right. An entero-anastomosis of the proximal loop to the distal loops was quickly made. The postoperative convalescence was uneventful, and the patient was dismissed cured.

This patient represents a rather mild condition of "duodenal intoxication." As this case was an early one in our series, the importance of renal functional studies was not appreciated. The urinalysis showed definite evidence of renal irritation. The early operative relief of the obstruction prevented the further development of renal injury. The alkalosis was definite.

DISCUSSION OF CLINICAL FINDINGS AND LABORATORY DATA

Etiology.—The eleven cases herein reported present a clinical syndrome supposedly typical of duodenal intoxication. Symptoms, probably those of gastric tetany, were present in all but one of the cases. Etiologically two types were represented;[24] those with demonstrable mechanical obstruction, and those without. We assume the latter to be due to functional stasis or a dynamic, or possibly intermittent obstruction. The cases in the first group included those of obstruction due to pyloric or duodenal ulcer, carcinoma, gastrojejunal ulcer and adhesions; those in the second group presented symptoms identical with those in the first, but adequate cause for obstruction could not be found by exploratory or necropsy examinations. The condition may be analagous or related to that in paralytic ileus. In this connection the cause of vomiting should be considered. The possibility of a toxic substance originating in the obstructed duodenum and stimulating the vomiting center cannot be ignored.

Gastric Symptoms.—The gastric symptoms were definite in both groups. Vomiting, although not invariably persistent, was present in all cases. In the chronically obstructed group, there were intermittent crises every few days with vomiting and the recovery of large amounts of thin, serous fluids. The emptying of the stomach was always followed by relief from symptoms for variable periods. In the postoperative group with acute obstructive symptoms, relief was less pronounced. The fluid loss in the gastric secretion varied from 600 to 6,000 c.c. in twenty-four hours. Epigastric pain was not a feature. Usually the patients complained only of mild distress in the epigastrium or of distention, which was relieved by belching or vomiting. The sharp colicky pains of lower intestinal closure were lacking. Nausea was usually absent.

Nervous Symptoms.—In our experience, in fatal cases, tetany or tetany-like symptoms usually developed in the course of toxemia. The

24. Renal injury from alkaline treatment of ulcer was not encountered in this group of cases except, possibly, in Case 2.

symptoms referable to heightened nerve irritability may be either motor or sensory in character. Several patients with chronic obstruction complained for years of vague pains and paresthesia, particularly in the extremities, during which the gastric symptoms were insignificant. Pain, tingling and twitchings of all degrees may be present. In acute cases (Case 8) the pain may be severe and simulate an acute inflammatory lesion. Spasmodic and convulsive stages of tetany were seen in the more severe toxemias and often represented terminal events. In this stage, we found evidence of renal injury and insufficiency.

Shock-like Features.[25]—The shock-like features of the syndrome may be related to the marked fluid loss, resulting from persistent vomiting. The low blood pressure, red facies,[26] high hemoglobin, asthenia, and low muttering delirium, denoted the severity of this fluid depletion. Maintenance of blood fluids is often impossible at this time. Keith has pointed out that in shock the vessel walls lose the capacity to retain fluids.[27] This condition apparently obtains also in some cases of duodenal toxemias. In seven of our cases, fluids were administered, such as salt and glucose solutions, in large amounts without demonstrable improvement. Transfusions or colloidal solutions were not employed.

Urinary Excretion.—The urine was usually scanty as a result of excessive loss of fluid from the stomach. The urine chlorids were greatly diminished. The concentration and dilution functions of the kidney were not definitely impaired in one case in which they were studied. Albumin, casts, and red blood cells were always found in the urine in the toxic stage.

Blood Chemistry.—The chemical changes in the blood and tissues were practically pathognomonic and are consequently of great diagnostic and prognostic significance. The decrease in plasma chlorids and the increase in the carbon dioxid combining power of the blood appeared first early in the development of the toxemia. When tetany

25. Gerard has recently compared the pharmocologic action of "obstruction fluid" and histamin. The shock features of duodenal toxemia and histamin poisoning are, in many respects, similar.

26. One of us (L.G.R.) has previously noted this red facies in patients with diabetes insipidus, to whom histamin was administered.

27. Keith has also produced experimental dehydration in dogs by injecting intravenously a calculated amount of 50 per cent. saccharose solution. By this method a marked diuresis accounted for an average loss of 11 per cent. of the body weight in a few hours. Definite and constant circulatory changes occurred during the period of dehydration. These were characterized by increased blood viscosity, raised hemoglobin concentration and a distinctly diminished circulating plasma volume. Shocklike features were not present. With the giving of an adequate amount of water by mouth, the circulation was rapidly restored to normal.

was definitely established, the acid-base balance was always disturbed, as demonstrated by an increase of the carbon dioxid combining power of the blood.[28] Murray[29] has found unchanged or only slightly changed values in the hydrogen-ion cencentration of the blood in experimental closure of the pylorus. This change in the acid-base equilibrium is probably due to excessive loss of acid in the gastric juice which may be an exaggerated phase of the normal carbon dioxid curve after meals. McCann[10] has observed experimentally that reestablishment of gastrojejunal continuity causes a decided decrease in the alkaline reserve of the blood. We noted a similar response in Case 7, following a drainage relief operation. It appears feasible, at least, that the loss of the hydrogen-ion in the gastric juice results in a relative increase of the blood bases. Chlorid depletion was observed early, and remarkably low values were observed in the blood plasma. An increase of plasma chlorids was observed in Case 7 as a result of reestablishment of gastrojejunal continuity. The chlorid depletion is probably due to loss of chlorids in the gastric juice. In only one instance was the increase of sodium in plasma found. The chlorid content of the tissues showed that an actual depletion existed and that fixation of chlorids, as in pneumonia, was not present. The chlorid values showed a relatively early change after the toxemia was established, and as noted in two of the patients, followed shortly after the disturbance in the alkaline reserve.

High levels for nonprotein nitrogen in the blood were observed in all our severe cases. High values were obtained for urea in the blood and corresponding increases in creatinin. Definite changes were noted in the acid-base balance and chlorid level in several cases in which stasis was relieved before the renal injury had progressed sufficiently to produce azotemia. We believe that while tissue destruction (catabolism) may be excessive, renal injury is an important factor. In cases in which the phenolsulphonephthalein test was given, the excretion of the substance was definitely decreased. The renal injury was grave, as shown by functional tests and necropsy examinations. Clinically, the renal lesion suggested a degenerative type similar to that so frequently seen in many forms of experimental nephritis. Edema, increased blood pressure and retinal changes were absent.

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28. Van Slyke has shown that the alkalosis is due to an alkali excess since the bicarbonate-carbonic acid ratio is disturbed in favor of the bicarbonate. When the hydrogen-ion concentration of the blood is undisturbed, he has designated the condition as a "compensated alkalosis."

29. Murray, H. A.: The Bicarbonate and Chloride Content of the Blood in Certain Cases of Persistent Vomiting, Proc. Soc. Exper. Biol. & Med. **19**: 273-275, 1922.

Pathologic Condition.—In the six cases ending fatally, pathologic examinations showed severe toxic nephritis.[30] The tubular epithelium revealed degenerative changes. Granular and fatty degeneration were uniformly present. No marked changes were seen in the glomeruli. When calcium had been administered as a therapeutic measure, deposits of this substance were found in the tubular epithelium. This is of interest in connection with the work of Bowler, who finds that excessive doses of calcium chlorid produce no toxic effect on the kidneys.[31] The urine contained albumin, casts and erythrocytes during the toxic stage. Marked dilatation of the stomach and duodenum were noted in all necropsy cases. Definite changes in the duodenal mucosa were seen in one case only (Case 10). The absence of gross pathologic changes in the mucosa does not militate against the assumption of Hartwell and others that changes in this tissue are an essential feature of the toxemia. Minor or functional changes may exist.

Correlation of Clinical and Laboratory Data.—It is difficult to determine to what extent certain symptoms are due to renal insufficiency or tetany. Uremia is characterized chiefly by symptoms referable to the gastro-intestinal and nervous systems and by asthenia. Such symptoms are present in duodenal toxemia. Our impression, perhaps without sufficient basis, has been that the earlier symptoms of this character were due to tetany. In the later stages, in the presence of proved renal insufficiency, we believe that the symptoms are at least partially uremic in origin. Such symptoms are daily encountered in cases of nephritis in the absence of tetany and even in the presence of acidosis. The renal injury may be present fairly early after the onset of the toxemia. Headaches are common. The mental aberration particularly suggests uremia. Consequently, we believe that the burden of proof should rest on those who hold that these symptoms are not uremic in origin.

The pathologic condition in the kidney is in keeping with the clinical and laboratory data. The rôle of the kidney cannot be disregarded, since the renal lesion is often the most outstanding pathologic finding at necropsy.

Diagnosis.—In the diagnosis of duodenal intoxication, the laboratory findings are of great importance and sometimes pathognomonic. In cases of duodenal ulcer with obstruction, vomiting is frequent, in both preoperative and postoperative stages. When, however, vomiting is marked or persistent, chemical studies of the blood are indicated, and especially when the vomiting is accompanied by florid facies and mani-

30. There was no evidence that a preexisting nephritis had been present in the cases coming to necropsy, differing in this respect from the cases reported by Tucker.

31. Personal communication.

festations of tetany or shock. The findings of increased carbon dioxid combining capacity of the plasma with low plasma chlorids indicate the existence of this toxemia. And when this is associated with evidence of renal insufficiency, as shown by increased blood urea with low phenolsulphonephthalein excretion, the diagnosis can be made with certainty. The extent of the damage is reflected in the degree of chemical disturbance.

Prognosis.—The preoperative and postoperative cases should be considered separately. In the preoperative group, the nature of the pathologic lesion is of paramount importance. The alkalosis is secondary, is of less consequence and more easily controlled. Aside from the alkalosis, chlorid depletion and renal insufficiency may be present and yet recovery be possible (Case 2). Had operation been undertaken in the presence of these findings to the neglect of preoperative medical treatment, the outcome would probably have been fatal. In determining the operative risk, the degree of renal involvement is important. Under the proper management, renal function may be reestablished in this condition, as happens quite frequently following relief of lower urinary tract obstruction. No sharp line of division can be drawn between the operative and nonoperative cases, but an attempt to improve renal function by suitable medical measures should be undertaken prior to operation. Palliative operations involving drainage may be desirable. A blood urea above 100 mg. for each 100 c.c. and a phenolsulphonephthalein excretion of 10 per cent. or less represents a poor surgical risk.

The postoperative cases are likely to prove more serious. The onset as a rule is more acute, the course more fulminating and death may occur before the seriousness of the condition is recognized. Relief of stasis may result in recovery if effected by either medical or surgical treatment before serious renal damage occurs. In both groups, the degree of renal injury is probably the determining factor. The advent of general convulsions or severe manifestations of tetany also indicate grave prognosis.

Treatment.—Obviously, in view of the obstructive origin of the toxemia the treatment is primarily surgical. The relief of the obstruction is the main objective, and consequently simple drainage operations may be desirable. When, however, surgical measures are associated with excessive risk, medical treatment may be necessary. In surgical interference, etherization is undesirable. According to the work of Dale [32] in histamin poisoning, resistance is markedly lowered by ether. On this basis, Gerard advocates the use of nitrous oxid and oxygen.

32. Dale, quoted by Gerard.

Medical treatment may be considered under the heading of: (1) drainage or mechanical relief, (2) administration of fluids, (3) dietary control, and (4) drug therapy. Drainage can be obtained by means of the stomach tube. Frequent lavage is essential. Dilute hydrochloric acid, 1 to 2 c.c., may be given through the stomach tube. When tetany exists, calcium chlorid 10 per cent. solution in doses of 1 to 2 gm. may be given in this manner or intravenously. Since excessive fluid is lost by vomiting and concentration of the blood results, large amounts of water are indicated. This can be administered in the form of physiologic saline solution intravenously, subcutaneously, or by rectum. Dragstedt has found that Ringer's solution is more effective than sodium chlorid solution in controlling experimental tetany. It proved of great value in one of our cases. Accumulation of nitrogen in the blood indicates a low protein and high carbohydrate diet. We have used farinaceous food and milk, to which lactose and cream have been added. Since the putrefactive bacteria flourish in an alkaline medium and, the aciduric flora in an acid medium, buttermilk, or *Bacillus acidophylus* milk may be tried.

Drugs are used to combat alkalosis and tetany. Dilute hydrochloric acid is given in 2 to 4 c.c. doses in sodium chlorid solution by rectum, or by mouth if obstruction is not complete. Five hundred cubic centimeters of 0.1 normal hydrochloric acid in 500 c.c. of physiologic saline solution has been used by Murray. Haldane[33] has recently shown that ammonium chlorid when given by mouth produces a decrease in the alkaline reserve of the blood and alveolar carbon dioxid.[34] In the light of recent knowledge on the toxicity of sodium bicarbonate, it is important to avoid it in gastric tetany and duodenal toxemia. In the medical treatment of duodenal ulcer, the condition of the kidney constantly followed nephritis, for Hardt and Rivers have shown that toxic symptoms appear at times within the first week of treatment before neutralization of the gastric juice or alkalinization of urine is effected.

SUMMARY

1. Eleven cases are reported in which as the result of organic obstruction, anatomic or physiologic stasis in the duodenum, duodenal toxemia developed.

2. Duodenal toxemia is characterized by a clinical syndrome, by urinary changes, by pathognomonic changes in the chemistry of the

33. Haldane, J. B. S.: Experiments on the Regulation of the Blood's Alkalinity, J. physiol. **55**:265-275, 1921.

34. McCann has given this method clinical trial in a case of gastric tetany, using 500 c.c. of an 0.822 per cent. solution of ammonium chlorid (hydrogen-ion concentration 7). The solution was previously tested for hemolysis against patients' blood. Tetany symptoms were relieved.

blood, by decreased renal function, and in case of death by pathologic changes in the kidney.

3. The clinical picture consists of: (1) vomiting of large amounts of a thin, serous, bile-stained fluid, (2) evidences of dehydration, red florid complexion, high hemoglobin, low blood pressure and asthenia, (3) by tetany-like manifestations, and (4) features of shock and uremia.

4. The blood shows: (1) a low level of chlorids, (2) a high carbon dioxid carrying capacity, and (3) a high level of blood urea and of creatinin.

5. Urinalysis reveals albuminuria and casts.

6. Renal functional studies indicate renal insufficiency, high values for urea and creatinin, and a decreased excretion of phenolsulphonephthalein.

7. Necropsy in six cases revealed the pathologic condition of nephrosis characterized either by acute degenerative changes in the tubular epithelium or by a diffuse nephritis.

8. Prognosis and treatment are discussed.

A CLINICAL REPORT ON ACUTE CASES OF MERCURIC CHLORID POISONING*

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Poisoning by mercuric chlorid is a condition of comparatively frequent occurrence at the present time, and the opportunity to study a considerable number of such cases has furnished data which seem of sufficient interest to justify a report. While some of these patients have been transferred to other hospitals within a comparatively short time after admission to the service, there have been a number which we have been able to study with a fair degree of thoroughness, and these have presented interesting findings.

Most of the work previously reported has been along therapeutic lines and has in the main tended to confirm the earlier general impression of a high mortality from this condition. Sansum [1] has reviewed particularly carefully the literature on the subject and has conducted animal experiments which seem to show that for dogs the minimum lethal dose is quite uniformly 4 mg. of mercuric chlorid intravenously per kilogram of body weight. A dose of 5 mg. per kilogram of body weight would quite regularly produce death with anuria, and his experiments tended to show that when anuria had been so caused, all attempts to reestablish the flow of urine by use of diuretic solutions failed. His figures correspond with those of various textbooks which give 3 to 5 grains (0.19 to 0.32 gm.) as the lethal dose for an adult. It is quite impossible to confirm these figures clinically, since it is frequently impossible to know the dose which has been taken and equally impossible to know the amount which has been removed by vomiting, gastric lavage and catharsis. It is probable that some persons are much more susceptible than others. This is suggested particularly by the considerable number of cases of poisoning recently reported as due to absorption from the vagina, either from douches of mercuric chlorid solution or from tablets placed in the vagina to prevent conception. The amount of mercurid chlorid used in this way is, as a rule, small. There are two sizes of tablets commonly sold for antiseptic purposes—the larger one is 7.8 grains (0.5 gm.) and the

* From the medical service of the Cook County Hospital. Read before the Chicago Society of Internal Medicine, May 29, 1922.

1. Sansum, W. D.: Principles of Treatment in Mercuric Chlorid Poisoning, J. A. M. A. **70**:824 (March 23) 1918.

smaller is 1.82 grains (0.1 gm.), and it would be necessary to assume absorption of approximately one half of one of the larger tablets or a corresponding number of smaller ones to explain death from this source. On the contrary, there are some patients who recover in spite of having apparently retained much more than the estimated minimum lethal dose. It is always, however, impossible to know how much mercury may have been removed and how much may have been rendered inert by material in the gastro-intestinal tract and passed out unabsorbed.

Mercuric chlorid poisoning furnishes an excellent opportunity to study the retention of nitrogenous waste products in the blood, and several such studies have been made [2] and the findings compared with those seen in other kidney lesions. Myers and Lough,[3] in their studies on nephritis, have emphasized particularly the prognostic value of the blood creatinin figures and have stated that figures of 3 to 5 mg. per 100 cubic centimeters are decidedly unfavorable and that amounts above 5 mg. probably mean early fatal termination. They have reported a fatal case showing: creatinin, 33.3 mg. per 100 cubic centimeters of blood; urea nitrogen, 240 mg.; and uric acid, 15 mg. Campbell,[4] on the other hand, believes that creatinin retention as a guide in prognosis is valuable only in chronic cases of kidney disease, and he cites one case of mercuric chlorid poisoning in which creatinin reached 12.5 mg. and recovery occurred. Underhill [5] reported recovery of a patient after urea nitrogen reached 240 mg.

Rosenbloom [6] reviewed the previous literature on the therapeutic measures and suggested a method of treatment which seems to combine the more effective measures of the various methods previously used. For the benefit of those who are not familiar with it, we would refer to the original article. The treatment includes the use of calcium sulphid, sodium phosphate and acetate, intravenous injection of Fischer's solution, colonic irrigations, hot packs, alkaline drinks and proctoclysis of potassium acetate, sodium bicarbonate and glucose, rest in bed, etc.

This treatment has been used in our service with comparatively little modification for the past eighteen months, and has seemed to give the most favorable results. It combines many of the measures previously

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2. Elwyn, H., and Flood, E. P.: Kidney Function in Case of Bichlorid Poisoning, Med. Rec. **98**:56 (July 10) 1920.

3. Myers, V. C., and Lough, W. G.: The Creatinin of the Blood in Nephritis. Its Diagnostic Value, Arch. Int. Med. **16**:536 (Oct.) 1915.

4. Campbell, W. R.: Observations on Acute Mercuric Chlorid Nephrosis, with a Report of Two Cases, Arch. Int. Med. **20**:919 (Dec.) 1917.

5. Underhill, A. J.: Blood Urea in Renal Conditions, New York M. J. **102**:662 (Sept. 25) 1915.

6. Rosenbloom: Acute Bichloride of Mercury Poisoning Treated by Newer Methods, Am. J. M. S. **157**:348 (March) 1919.

used and thus involves a considerable amount of time and effort. Lavage is continued until the washings are reported free from mercury. If this method has advantages over those previously used, they are probably dependent on the amount of mercury removed by the repeated lavage, as shown in case records contained in the tables. In one such case, mercury was found in the washings as late as eleven days after being taken and was present in considerable quantities during the early days of treatment. It is probable that a good deal of mercury is removed in this way, and it is to be hoped that later we may have quantitative determinations of the mercury so removed. To date this has not been possible.

From Jan. 1, 1920, to May 1, 1922, there have been admitted to the Cook County Hospital to all services a total of seventy-one cases of mercuric chlorid poisoning, distributed as shown in Table 1.

TABLE 1.—*Cases of Mercuric Chlorid Poisoning at Cook County Hospital from Jan. 1, 1920, to May 1, 1922*

	Total	Recovered	Died	Mortality Percentage
1920	26	24	2	7.7
1921	35	28	7	20.0
1922	10	8	2	20.0
Total	71	60	11	15.5

Of this number, thirty have been admitted to our service. The results are shown in Table 2.

It will be noted that all cases in this series from No. 750145 to the end of the table showed positive tests for mercury in the stomach contents or urine or both. Prior to January, 1921, such examinations were not available, but only unquestioned cases have been included in the series. It has at times happened that patients have feigned poisoning with mercuric chlorid, but any such cases have been carefully excluded. When such cases arise they should be treated as cases of mercuric chlorid poisoning until repeated tests have demonstrated that no mercury is present, since it is also not unusual for one who has taken mercuric chlorid to deny it vigorously until told that chemical examination of the stomach contents reveals the poison.

Two of the patients in the twenty-seven cases here tabulated died in this hospital. Twelve of these patients were brought into the County Hospital as emergency cases and were transferred to other hospitals when friends or relatives became cognizant of their presence in the hospital. In this way a number of patients have been lost to observation before a sufficient period has passed to enable us to be certain of the outcome.

One patient (M. K.) who left the hospital at the end of fourteen days very much improved, died at her home within two or three days under circumstances which suggest that she had probably taken a

TABLE 2.—*Results with Rosenbloom's Method of Treatment and Former Methods of Treatment in Authors' Cases*

Case No.	Age	Previous Health	Dose of Mercuric Chlorid	Mercury in Stomach Contents	Vomiting	First Treatment	Entered Hospital	Treatment	Days in Hospital	Result
720406 M. K.	24	Good	15.6 gr.	—	15 min.	Immediately	2 hr.	G	2	Improved (Rel)
720604 G. J.	22	Good	20 gr.	—	30 min.	30 min.	1 hr.	G	10	Recovery
729661 K. R.	28	Good	?	—	No	1 hr.	3 hr.	G	3	Recovery
733012 A. N.	28	Pregnant	30 gr.	—	15 min.	1 hr.	1 hr.	G	5	Improved (Rel)
738297 L. R.	26	Pregnant	15.6 gr.	—	No ?	2 hr.	2 hr.	G	1	Rel.
738329 E. M.	20	Good	1.8 gr.	—	15 min.	15 min.	15 min.	G	1	Rel.
738596 V. K.	24	—	30 gr.?	—	15 min.	.....	1½ hr.	G	1	Rel.
743400 A. O.	22	Alcoholism	?	—	Soon	?	?	G	—1	Rel.
743782 J. O'B.	21	Poor	4 tabs. size ?	—	Immediately	—	1 hr.	G	—1	Rel.
750145 N. R. B.	24	—	7 tabs.	+	10 min.	10 min.	45 min.	R	16	Recovery
750976 V. S.	22	Good	?	+	10 min.	—	1 hr.	R	10	Recovery
753486 E. B.	26	—	10 tabs.	+	No	—	2 hr.	R	7	Recovery
755156 S. S.	20	—	6 tabs. size ?	+	—	20 min.	20 min.	G	2	Rel.
758244 J. B.	29	—	Bottle of tablets	+	Soon	Many hours	5 days	G	3	Died
764043 L. O'R.	40	—	40 gr.	+	30 min.	30 min.	7 hr.	G	3	Improved (Rel)
764448 R. M.	19	Skin lesion on leg	?	+	No	?	Many hours	G	4	Improved
766305 J. S. H.	41	Good	?	++	—	30 min.	4 hr	R	4	Rel., improved
766586 M. I.	40	—	11 tabs. size ?	+++	4 hr.	—	28 hr.	R	13	Died
766759 M. K.	40	—	?	++	30 min.	30 min.	1½ hr.	R	14	Recovery
766980 C. M.	29	25 tabs. size ?	25 tabs. size ?	+++	Few min.	30 min.	1 hr.	R	36	Recovery
772721 F. L.	21	Syphilis	4 tabs.	+	30 min.	30 min.	5 hr.	R	13	Recovery (Rel)
773174 A. S.	62	Diabetes, morph. nephritis	5 tabs.	+++	Immediately	—	3 hr.	R	8	Improved (Rel)
777363 E. G.	—	Good	5 tabs.	+	30 min.	30 min.	1 hr.	R	7	Recovery
784846 L. B.	22	Good, alcoholic	?	+++	30 min.	30 min.	1½ hr.	R	12	Recovery
785329 O. S.	18	Mental dis.	6 tabs.	+	Few min.	30 min.	1½ hr.	R	14	Recovery, trans. to psycho.
785439 C. H.	16	Good	1 tab.	Tr.	15 min.	15 min.	4 hr.	R	14	Recovery
787296 H. D.	21	Pyelitis, gynecol.	3 tabs. 23.4 gr.	++	10 min.	30 min.	24 hr.	R	9	Recovery, trans. to psycho.

G indicates general methods of treatment formerly in use; R, method of treatment outlined by Rosenbloom; Rel, released to the care of relatives or friends. Such patients were usually transferred to private hospitals for further care.

further dose of poison after leaving the hospital, but definite information on this point was not obtainable. Since that time it has become our practice to have all such patients examined by the psychopathic department before discharge.

Most of the other patients included in this series left the hospital recovered or in such condition that recovery seemed assured, and careful search of records of the coroner's office shows no report of deaths other than those here recorded.

ILLUSTRATIVE CASES

The following cases present features of special interest and are therefore presented in greater detail than the previous tables permit.

CASE 1.—Margaret I. (No. 766586), aged 40, weight approximately 135 pounds (61.2 kg.), was admitted to the hospital on July 16, 1921, at 10 p. m., with a history of having taken eleven tablets of mercuric chlorid (probably 20.02 grains) twenty-eight hours previously. The patient had vomited repeatedly and was having frequent involuntary defecations. Examination of the stomach washings on admission showed considerable quantities of mercury, and mercury continued to be present in every specimen of stomach washings up to and including the eleventh day. The patient was catheterized repeatedly, and no urine was obtained until the fourth day in the hospital, when 10 c.c. were obtained, as shown in the accompanying table. She reported that she passed small amounts of urine at the time of bowel movements during the next few days, but although she was catheterized no further urine was obtained for examination, until the tenth day.

TABLE 3.—*Blood Chemistry in Case 1*

	Day				
	Second	Fourth	Sixth	Eleventh	Fourteenth
Urea nitrogen	33.02	53.70	73.60	92.00	116.00
Urea	71.94	113.42	157.50	196.80	248.20
Uric acid	4.16	4.21	6.21	8.27	8.93
Creatinin	4.27	6.11	8.87	10.19	11.37

TABLE 4.—*Urine Examinations in Case 1*

Day	Amount	How Obtained	Color	Reaction	Albumin	Sugar	Blood	Pus	Casts
2	0	Catheterization	.....	.....	..	..	..	..	..
4	10 c.c.	Catheterization	Straw	Acid	..	0	0	..	0
6	Trace	Lost with stool account of diarrhea.	No specimen obtainable						
7	Trace	Lost with stool account of diarrhea							
8	Trace	Lost with stool account of diarrhea							
9	0	Catheterization	.....	.....	..	..	..	..	..
10	15 c.c.?	Spontaneously	Straw	Acid	..	0	0	..	Occasional hyaline
13	.....	Lost with stool							

Rosenbloom treatment as previously outlined was instituted immediately on admission to the hospital. So far as could be ascertained, no treatment had been instituted prior to the patient's admission to the hospital. This patient, therefore, presents a longer interval before treatment than any of the other cases in the series, and though the dose of poison taken was much less than that from which other patients in the series recovered, the patient died on July 29, 1921, thirteen days after admission.

CASE 2.—Carrie M. (No. 766980), aged 29, weight approximately 150 pounds (68 kg.), was admitted to the hospital on July 20, 1921, at 5 p. m. She had swallowed twenty-five mercuric chlorid tablets at 4 p. m., and within thirty minutes milk had been given and vomiting induced. On entering the hospital she continually vomited blood streaked material which gave a strong test for mercury, and mercury was found in the stomach washings each day up to and including the sixth day. A trace of mercury was found in the urine as late as the fourteenth day. From the outset the patient was unable to void, and no urine was obtained on catheterization. The first urine was obtained on the seventh day, and from that time steadily increasing quantities were passed, although some of the first specimens were lost in expelling enemas, and it was impossible to obtain reliable data concerning the twenty-four hour output. The nitrogen retention reached its maximum on the eleventh day, as shown in the tabulated blood chemistry determinations, and from that time improvement was rapid. The patient remained in the hospital for thirty-six days and left the hospital apparently entirely recovered. She has been out of the city most of the time during the past year but has reported that urinalysis showed no abnormality and that she has been in good health.

TABLE 5.—*Blood Chemistry in Case 2*

	Day							
	First	Third	Eleventh	Fifteenth	Nineteenth	Twenty-Second	Twenty-Seventh	Thirty Third
Urea nitrogen.....	22.41	40.00	70.05	64.91	40.62	22.54	18.21	17.02
Urea.....	49.95	85.60	149.80	136.96	86.92	48.33	38.96	36.42
Uric acid.....	4.21	4.21	12.50	9.71	5.15	2.45	2.11	2.31
Creatinin.....	3.75	3.50	13.10	11.27	3.33	1.87	1.55	1.49
Sugar.....	191	97	95	141	—	—	—	—

TABLE 6.—*Urine Examinations*

Day	Color	Specific Gravity	Reaction	Albumin	Sugar	Blood	Leukocytes	Casts	Remarks
7	Straw	?	Alkaline	0	0	0	+	0	3 c.c. only
11	Straw	1.009	Alkaline	0	0	0	0	0	
13	Straw	1.010	Alkaline	0	0	0	0	0	
14	Straw	1.014	Alkaline	++	0	0	0	0	
15	Straw	1.010	Alkaline	++	0	0	0	0	
20	Straw	1.010	Alkaline	Trace	0	0	+++	0	
25	Amber	1.010	Alkaline	0	0	0	++	0	
26	Amber	1.011	Acid	0	0	0	+++	0	
27	Straw	1.012	Acid	0	0	0	++	0	
32	Straw	1.012	Alkaline	0	0	0	0	0	
34	Amber	1.011	Acid	0	0	0	+	0	

CASE 3.—Olga S. (No. 785329), aged 18, who weighed approximately 125 pounds (56.6 kg.), was admitted to the hospital on Jan. 20, 1922, at 12:10 a. m., having swallowed six tablets (size unknown) of mercuric chlorid at 10:30 p. m. One half hour after taking poison she drank milk and vomited. Chemical examination revealed mercury in the stomach washings on the first, second and third days, and in the urine up to the fourth day. The patient was put at once on the Rosenbloom treatment as outlined, and made an uneventful recovery from the poisoning, being transferred on the fourteenth day to the Psychopathic Hospital for further observation because of a psychosis. This patient showed albumin and casts persistently present in the urine. No history of previous kidney disease was obtained. It is interesting to note that albumin and casts are by no means uniformly found in cases of mercuric chlorid poisoning, and even some of the more severe cases have shown albumin only for comparatively short periods.

TABLE 7.—*Blood Chemistry*

Day	Urea Nitrogen	Urea	Creatinin
2	19.61	41.96	1.51
6	13.07	27.96	....

TABLE 8.—*Urine Examinations*

Day	Appearance	Specific Gravity	Reaction	Albumin	Sugar	Leukocytosis	Casts
1	Clear	1.020	Alkaline	++	0	Few	Many granular
3	Cloudy	1.028	Acid	+++	0	++	Many granular
4	Cloudy	1.010	Alkaline	++	0	++	Few granular
5	Cloudy	.....	Alkaline	+	0	++	Few granular

DISCUSSION

For a long time there has apparently been a general impression both among the laity and in medical literature that mercuric chlorid poisoning is almost uniformly fatal. This view has been strengthened by the researches of Meyer and Gottlieb, and of Sansum; particularly by the work of the latter concerning the uniformity of the minimum lethal dose when mercuric chlorid is given intravenously to dogs. Conditions for absorption of this poison when taken by mouth, however, are quite different from those observed experimentally, and from our observations it is quite evident that patients in whom the prognosis *a priori* appears bad, either because of large dose or late treatment, may recover. It is therefore essential that all patients be treated carefully even though conditions appear most unfavorable for recovery—as, for example, in the case of C. M. with prolonged anuria, high nitrogen retention, etc.

The aim of therapy is to block every possible avenue of absorption and to remove from the body as much mercury as possible. In our experience this has seemed to be best accomplished with the method of Rosenbloom. It is especially interesting to note the long period in which we have continued to obtain mercury in stomach washings. It is to be regretted that we have been unable to obtain quantitative analyses of the mercury thus removed. It would seem that in many cases the amount is considerable and that it might readily, in some cases at least, make the difference between a lethal and nonlethal dose. It seems quite essential that the washings should be tested for mercury and the treatment continued until it is quite certain that no further mercury will be removed in this way.

Blood chemistry determinations have furnished much interesting data and would seem to be of some value in prognosis. These figures, however, do not have in mercuric chlorid poisoning the same significance

as in the other kidney lesions in which they have been most studied. Low grade nitrogen retention bespeaks recovery, but high figures do not necessarily mean a fatal termination (see C. M.). The value of the creatinin test, which has been particularly advocated, as a prognostic sign is much greater in chronic kidney disease than in acute conditions comparable to the one herein observed. This is in agreement with the previous report of Campbell.

STUDIES IN FAMILIAL NEUROSYPHILIS

III. CONJUGAL NEUROSYPHILIS (SECOND COMMUNICATION)*

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In the first paper of this series [1] we outlined the methods employed in and reported the results of the examinations of fifty-two marital partners of fifty neurosyphilitic persons, with the thought that the data thus obtained might be of value in the debate as to the existence of a neurotropic strain of *Spirochaeta pallida*. It was recognized that the family material employed in such a study must be as nearly as possible unselected and that the methods of examination must include not only the usual Wassermann survey, or physical and neurologic examination, but also, in view of our increasing knowledge of asymptomatic neurosyphilis, all these procedures plus routine examination of the cerebrospinal fluid of every available marital partner of a series of neurosyphilitic patients. The value of this method of approach was indicated by the discovery of asymptomatic neurosyphilis in seven marital partners, the abnormal spinal fluid findings being the sole indication of syphilis in three of these.

Although the literature contained many reports of series of families with conjugal neurosyphilis and a few excellent studies of routine physical or Wassermann examinations of the marital partners of neurosyphilitic persons, we were unable to find any communications in which the data given were strictly comparable to our own; and since the date of our publication (July, 1921) no further satisfactory studies have appeared.

Owing to the comparatively small number of families reported in our first paper, no definite conclusions as to the duality of strain of *Spirochaeta pallida* were permissible. It did appear, however, that conjugal neurosyphilis was of relatively frequent occurrence. It was noted to be more common among the partners of parenchymatous

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1. Moore, J. E., and Keidel, A.: Studies in Familial Neurosyphilis. I. Conjugal Neurosyphilis, J. A. M. A. **77**:1 (July 2) 1921.

neurosyphilitic persons than among those married to patients with diffuse cerebrospinal (meningovascular) neurosyphilis.[2] This fact, together with other differences between the two groups, led us to suggest the possibility of the existence of two neurotropic strains of the organism, the lesions caused by one of these being largely confined to the nervous system (parenchymatous type).

The practical and probable scientific value of the study has led us to continue the work during the past two years. An additional sixty-one families have now been studied from this point of view, making a total of 111 families at our disposal. In this paper will be reported the details of the recent sixty-one families, together with a summary of the whole series. The unselected character of the material is emphasized; as each neurosyphilitic patient enters the clinic he is urged to bring his spouse in for examination. Only those marital partners in whom are obtainable anamnesis, physical and neurologic examination, blood Wassermann tests, and spinal fluid study are included, the absence of any one of these rendering the case too incomplete for consideration. These data are also available in the original patient.

Of the sixty-one new families, the original member (not always the one to acquire syphilis and introduce it into the family) was paretic in fourteen instances, tabetic in seventeen, and in thirty instances had cerebrospinal syphilis (early or late). The material will be considered under these headings.

GENERAL PARALYSIS

In Table 1 are summed up the details of the examination of the marital partners of fourteen paretic patients. Six of these were apparently normal; eight, or 57.1 per cent., were syphilitic. Of these, three were neurosyphilitic, in two instances (and probably the third) the neurosyphilis being of the parenchymatous type. Clinical neurosyphilis was also present in the wives of two other paretic men, the families not being included in the tables because of the lack of spinal fluid examinations. In Family 74, neurosyphilis was detected only by the routine use of spinal puncture.

2. In this paper the term parenchymatous neurosyphilis includes general paresis, tabes dorsalis, and taboparesis. Other neurosyphilitic diseases are classified under the general heading of cerebrospinal syphilis, the descriptive terms meningeal, vascular, meningovascular, neurorecurrence, asymptomatic, etc., being used when possible. In many cases the neurologic abnormalities will not permit accurate localization of the lesions; these cases, in our nomenclature, are referred to as syphilis C. N. S. unclassified, or diffuse cerebrospinal syphilis.

TABLE 1.—*Group of Families with General Paresis*

Family Number	Person Introducing Syphilis	Diagnosis in Person Introducing Syphilis	Duration of Syphilis, Years	Duration of Marriage, Years	Condition of Partner (Wife or Husband)							Diagnosis in Partner
					History of Syphilis	Physical Examination	Blood Wassermann Test	Cerebrospinal Fluid				
								Cells	Globulin	Wassermann Test	Colloidal Tests	
72	Husband	General paralysis	12	8	None	Negative	0	3	0	0	Negative	Nonsyphilitic
73	Husband	General paralysis	?	12	Three miscarriages	Gumma of tongue; neurologic examination negative	4	3	0	0	Negative	Tertiary syphilis
74	Husband	General paralysis	?	6	None	Negative	4	?	+++	4	Paretic	Cerebrospinal syphilis, asymptomatic
75	Husband	General paralysis	?	6	Indefinite history of rash	Negative	0	0	0	0	Negative	Nonsyphilitic
76	Husband	General paralysis	?	4	None	Negative	4	2	0	0	Negative	Syphilis (Wassermann)
77	Husband	General paralysis	20	13	None	Unequal, irregular pupils	4	1	0	0	Negative	Syphilis (Wassermann)
78	Husband	General paralysis	?	17	Rash 3 months after marriage	Pupils sluggish to light	4	0	0	0	Negative	Syphilis (Wassermann)
79	Husband	General paralysis	5	20	None	Negative	0	0	0	0	Negative	Nonsyphilitic
80	Husband	General paralysis	12	1½	Vague history of rash	Negative	4	2	0	0	Negative	Syphilis (Wassermann)
81	Husband	General paralysis	?	5	None	Negative	0	?	0	0	Negative	Nonsyphilitic
82	Wife	General paralysis	?	16	None	Negative	0	1	0	0	Negative	Nonsyphilitic
85	Husband	General paralysis	?	5	None	Unequal, sluggish pupils; knee jerks and ankle reflexes absent; Romberg sign +	0	3	+	0	Negative	Cerebrospinal syphilis, tabes
86	Husband	General paralysis	?	14	Rash and alopecia shortly after marriage	Irregular pupils; Romberg +; speech and memory defect	4	3	+	4	Paretic	Cerebrospinal syphilis, general paresis
87	Husband	General paralysis	29	10	None	Negative	0	3	0	0	Negative	Nonsyphilitic

A comparison of these families with the twenty-one families discussed in our earlier paper appears in Table 2. The data show discrepancies, probably explainable on the basis of the small number of families in each group. In the total, thirty-five families, one third of the partners were normal; two thirds were syphilitic, and of the syphilitic partners, 58.3 per cent. had neurosyphilis. In the fourteen partners with neurosyphilis, the type of the disease was certainly or probably parenchymatous (as in the original patient) in eleven instances.

TABES

The seventeen new families of tabetic patients are shown in Table 3. Nine of the marital partners were normal; eight, or about one half, had syphilis. Of the latter, four, or 50 per cent., were neurosyphilitic. Here, however, the type of neurosyphilis was the same as in the person who introduced syphilis into the family in only one instance (Family 103).

TABLE 2.—*Summary of Families with General Paresis*

	Number of Families	Number of Partners Investigated	Number of Partners Normal	Total Number of Partners Syphilitic	Percentage of Partners Syphilitic	Partners Probably or Certainly Neurosyphilitic	Percentage of Syphilitic Partners with Neurosyphilis
Moore and Keidel...	21	22	6	16	72.7	11	68.7
This study.....	14	14	6	8	57.1	3	37.5
Total.....	35	36	12	24	66.6	14	58.3

A comparison of the whole number of tabetic families, shown in Table 4, with the series of paretic families in Table 2, shows striking similarities. The incidence of syphilis in the partners of the two groups is about the same, and the incidence of neurosyphilis among the syphilitic partners almost precisely so. More than half of the syphilitic marital partners of patients with parenchymatous neurosyphilis were themselves neurosyphilitic.

CEREBROSPINAL SYPHILIS GROUP

This group of patients, which in our first communication was considered as a whole, has here been split into two parts to facilitate discussion. The first subgroup includes those families in which one member was found to be neurosyphilitic, either by clinical evidence or by routine spinal puncture, within the first eighteen months of his infection. The second is made up from families in which the original member, having had syphilis for some years, was found to have clinical cerebrospinal syphilis of various types on admission. The tables and

TABLE 3.—*Group of Families with Tabes*

Family Number	Person Introducing Syphilis	Diagnosis in Person Introducing Syphilis	Duration of Syphilis, Months	Duration of Marriage, Years	Condition of Partner (Wife or Husband)							Diagnosis in Partner
					History of Syphilis	Physical Examination	Blood Wassermann Test	Cerebrospinal Fluid				
								Cells	Globulin	Wassermann Test	Colloidal Tests	
88	Husband	Tabes	6	2	None	Negative	0	2	0	0	Negative	Nonsyphilitic
89	Husband	Tabes	14	32	None	Unequal, irregular pupils; reflexes hyperactive	0	3	+	0	Negative	Cerebrospinal syphilis, unclassed (?)
90	Husband	Tabes	?	18	None	Negative	0	2	0	0	Negative	Nonsyphilitic
91	Husband	Tabes	20	18	None	Irregular pupils; otherwise normal	4	7	0	0	Negative	Syphilis (Wassermann)
92	Husband	Tabes	26	17	None	Negative	0	1	0	0	Negative	Nonsyphilitic
93	Husband	Tabes	?	?	Vague	Negative	0	2	0	0	Negative	Nonsyphilitic
94	Husband	Tabes	17	7	None	Gumma soft palate	4	0	0	0	Negative	Nonsyphilitic
95	Wife	Tabes	?	10	Primary 8 years ago	Unequal, irregular pupils	4	10	+++	4	Paretic	Cerebrospinal syphilis, unclassed
96	Husband	Tabes	?	?	None	Negative	0	0	0	0	Negative	Nonsyphilitic
97	Husband	Tabes	?	25	None	Negative	0	0	0	0	Negative	Nonsyphilitic
98	Husband	Tabes	10	5	None	Negative	0	0	0	0	Negative	Nonsyphilitic
99	Husband	Tabes	20	16	Has borne a child with congenital syphilis	Negative	0	0	0	0	Negative	Syphilis, history
102	Husband	Tabes	?	22	None	Negative	0	0	0	0	Negative	Nonsyphilitic
103	Husband	Tabes	16	14	None	Optic atrophy	4	7	+	4	Paretic	Cerebrospinal syphilis, unclassed
105	Husband	Tabes	24	33	None	Irregular pupils; reflexes hyperactive	4	?	++	4	Low paretic	Cerebrospinal syphilis, unclassed
106	Wife	Tabes	?	14	None	Negative	0	0	0	0	Negative	Nonsyphilitic
123	Wife	Tabes	?	15	None	Slight difference in deep reflexes	4	4	0	0	Negative	Syphilis (Wassermann)

descriptions include twenty-one families from our first communication and thirty additional families, the earlier data being purposely repeated because of the regrouping.

EARLY CEREBROSPINAL SYPHILIS

Included in this group, details of which are shown in Table 5, are five families from our first paper (Families 17, 28, 12, 45 and 52) and thirteen additional families. Particular interest attaches to this group, since the entrance of syphilis into the family is recent, the duration of infection in husband and wife approximately the same, and since in one member early invasion of the nervous system by the organism had been detected. As may be seen from a study of the table, in each instance the one who introduced syphilis had recently contracted the disease and was usually first seen with the lesions of primary or secondary syphilis. The average duration of infection in the original patient was five and nine-tenths months. In these families, it is certain that the strain of organism infecting husband and wife is

TABLE 4.—*Summary of Families with Tabes*

	Number of Families	Number of Partners Investigated	Number of Partners Normal	Total Number of Partners Syphilitic	Percentage of Partners Syphilitic	Partners Probably or Certainly Neurosyphilitic	Percentage of Syphilitic Partners with Neurosyphilis
Moore and Keidel...	8	8	2	6	75.0	4	66.6
This study.....	17	17	9	8	47.0	4	50.0
Total.....	25	25	11	14	57.1	8	57.1

the same. If the fact of early nervous system invasion in one member be considered as evidence of neurotropism of the spirochete, neurosyphilis ought to be frequent among the marital partners. This statement, of course, disregards other factors, such as the kind and amount of early treatment, the patients' immune processes, etc., which may, and certainly do, influence the outcome. Contrary to expectation, however, neurosyphilis in the marital partners of this group is uncommon.

Of the eighteen partners, only three were normal. As the one introducing syphilis had recently had infectious lesions, fifteen were syphilitic, all of whom had acquired the disease but a short time before examination. In fourteen of the eighteen families, the member with the original infection was neurosyphilitic, the neurosyphilis being asymptomatic eight times, of the neurorecurrence type four times, and clinical neurosyphilis (without previous insufficient treatment) twice. Eleven of the fourteen partners of these patients had syphilis, of whom, however, only three were neurosyphilitic.

In Family 12, the one who introduced syphilis developed an eighth nerve neurorecurrence after insufficient treatment; his wife, with no

TABLE 5.—*Group of Families with Early Cerebrospinal Syphilis (Syphilis of Less Than Eighteen Months' Duration in Family)*

Family Number	Person Introducing Syphilis	Diagnosis in Person Introducing Syphilis	Duration of Syphilis, Months	Duration of Marriage, Years	Condition of Partner (Wife or Husband)							Diagnosis in Partner
					History of Syphilis	Physical Examination	Blood Wassermann Test	Cerebrospinal Fluid				
								Cells	Globulin	Wassermann Test	Colloidal Tests	
17	Wife	Cerebrospinal syphilis, asymptomatic	12	13	Infected 5 months before wife, whose spinal fluid was found routinely positive	Recurrent secondary rash; no neurologic signs	4	2	0	0	Negative	Recurrent secondary syphilis
28	Husband	Cerebrospinal syphilis, asymptomatic	4	2	Developed secondary syphilis concurrently with husband	Maculopapular rash; palmar syphilid; no neurologic signs	4	0	0	0	Negative	Early secondary syphilis
12	Husband	Neurorecurrence; left neuroretinitis, bilateral eighth nerve	15	1	None	Right facial paralysis, 1 week	4	18	++	4	Syphilitic zone	Meningeal neurosyphilis
45	Husband	Cerebrospinal syphilis, meningeal	?	6	Five years after marriage, secondary syphilis	Negative except for signs of secondary syphilis	4	2	0	0	Negative	Early secondary syphilis
52	Wife	Cerebrospinal syphilis, asymptomatic	?	½	Four months ago primary, followed by secondary lesions	Lesions of secondary syphilis; no neurologic signs	4	16	+	0	Syphilitic zone	Secondary syphilis and asymptomatic cerebrospinal syphilis
108	Husband	Primary, cerebrospinal syphilis, asymptomatic	1¼	13	None	Negative	0	0	0	0	Negative	Nonsyphilitic
109	Husband	Secondary, cerebrospinal syphilis, asymptomatic	6	1	General sore 5 months ago	Negative	4	0	0	0	Negative	Syphilis, Wassermann (early)
110	Wife	Secondary, cerebrospinal syphilis, asymptomatic	2	1½	None	Negative	0	0	0	0	Negative	Nonsyphilitic
111	Wife	Secondary, cerebrospinal syphilis, asymptomatic	6	1½	None	Macular syphilid	4	0	0	0	Negative	Early secondary syphilis
112	Husband	Secondary, cerebrospinal syphilis, asymptomatic	5	8	None	Negative	0	0	0	0	Negative	Nonsyphilitic
113	Husband	Acute syphilitic meningitis	6	5	Genital sore for 1 month	Roseola	4	0	0	0	Negative	Early secondary syphilis
114	Husband	Cerebrospinal syphilis, unclassed	8	?	Genital sore 6 months ago	Annular syphilid	4	0	0	0	Negative	Early secondary syphilis
115	Husband	Neurorecurrence; second and eighth nerves	7	3	Rash for 10 days	Pustular syphilid	4	0	0	0	Negative	Early secondary syphilis
116	Husband	Cerebrospinal syphilis, unclassed	12	½	None	Wassermann test positive on admission; developed a neurorecurrence after lapse in treatment	4	0	0	0	Negative	Cerebrospinal syphilis, neuroretinitis
118*	Husband	Primary syphilis; cerebrospinal fluid negative	1	6	None	Pupils sluggish	4	?	1+	4	Paretic	Asymptomatic cerebrospinal syphilis
119*	Husband	Secondary syphilis, cerebrospinal fluid negative	2	2	None	Negative	4	6	+	4	Paretic	Asymptomatic cerebrospinal syphilis
107	Husband	Primary syphilis; cerebrospinal fluid negative	2	1	Rash for 2 months	Secondary syphilis; lapse after insufficient treatment; neurorecurrence; bilateral eighth nerve involvement	4	4	+	4	Paretic	Cerebrospinal syphilis, neurorecurrence
120	Wife	Syphilis, Wassermann; cerebrospinal fluid negative	?	½	None	Mucous patches in throat; unequal, irregular, sluggish pupils	4	6	+	0	Paretic	Asymptomatic cerebrospinal syphilis

history of early syphilis or treatment, at the same time had a right facial paralysis of one week's duration and a positive cerebrospinal fluid. In Family 52, husband and wife, both with early syphilis, were discovered to have spinal fluid abnormalities of the same type (Group 2 of our classification of early asymptomatic neurosyphilis).[3] The husband in Family 116 showed definite clinical evidence of neurosyphilis and a positive spinal fluid on admission; his wife developed a neuro-recurrence involving the optic nerve after insufficient treatment.

In the last four families of the table (118, 119, 107 and 120), the one who introduced syphilis was normal from the neurologic standpoint, while his marital partner whom he had infected developed asymptomatic neurosyphilis. It is of particular interest that the husbands in Families 118 and 119 were infected by the same prostitute; neither of them developed neurosyphilis, but in both families the wives had positive spinal fluids without clinical signs.

LATE CEREBROSPINAL SYPHILIS

In Table 6 appear the data regarding this group of families, sixteen of which are transferred from our first paper (No. 51 and below), while seventeen are new. Of the thirty-four marital partners of thirty-three neurosyphilitic persons, nine were normal and twenty-five, or 73.5 per cent., were syphilitic. Seven of the syphilitic partners, or 28 per cent., had neurosyphilis. In four families (71, 60, 67 and 62), the one introducing syphilis did not show any evidence of nervous system damage, although the infected partner was neurosyphilitic The type of neurosyphilis in the partner was roughly similar to that in the original patient in two families, dissimilar in one, and asymptomatic in the remaining four.

A summary of the families with early and late cerebrospinal syphilis is given in Table 7. Striking differences from the parenchymatous group, both as to the incidence of syphilis and of neurosyphilis in the partners, are evident. Further attention will be directed to this point.

TYPES OF CONJUGAL NEUROSYPHILIS IN MARITAL PARTNERS

The value of routine spinal puncture in this type of study is admirably shown by the data summed up in Table 8. Of thirty-two cases of neurosyphilis in marital partners, no less than nine, or 26.1 per cent., would have been overlooked had not this procedure been employed. It is further evident that conjugal neurosyphilis of the same general clinical type is fairly common. The asymptomatic part-

3. Moore, J. E.: Studies in Asymptomatic Neurosyphilis. II. The Classification, Treatment, and Prognosis of Early Asymptomatic Neurosyphilis, Bull. Johns Hopkins Hosp. **33**:231, 1922.

TABLE 6.—*Group of Families with Late Cerebrospinal Syphilis (Duration of Disease in Family More Than Two Years)*

Family Number	Person Introducing Syphilis	Diagnosis in Person Introducing Syphilis	Duration of Syphilis, Years	Duration of Marriage, Years	Condition of Partner (Wife or Husband)							Diagnosis in Partner
					History of Syphilis	Physical Examination	Blood Wassermann Test	Cerebrospinal Fluid				
								Cells	Globulin	Wassermann Test	Colloidal Tests	
1	Husband	Vascular: epilepsy	?	3½	Late secondary rash 6 months after husband's nervous symptoms	Negative	4	3	0	0	Negative	Syphilis (Wassermann)
6	Husband	Vascular: hemiparesis	2	2	Primary syphilis 2 months after husband's primary	Mydriasis, otherwise negative	0	8	0	0	Negative	Latent syphilis
25	Husband	Vascular: hemiparesis	14	16	Negative	Anisocoria, sluggish pupils; auditory hallucinations	4	112	+++	4	Paretic	General paresis
36	Husband	Vascular: hemiparesis	4	2	Negative	Negative	4	2	0	0	Negative	Syphilis (Wassermann)
2	Husband	Cerebrospinal syphilis, unclassed	6	8	Negative	Negative	0	0	0	0	Negative	Nonsyphilitic
3	Husband	Cerebrospinal syphilis, unclassed	4	15	Secondary rash after husband's infection	Negative	4	0	0	0	Negative	Syphilis (Wassermann)
4	Husband	Cerebrospinal syphilis, unclassed	9	6	Negative	Negative	0	0	0	0	Negative	Nonsyphilitic
14	Husband	Cerebrospinal syphilis, unclassed	4	3	Doubtful history of rash	Negative	4	27	+++	4	Paretic	Asymptomatic neurosyphilis
19	Husband	Cerebrospinal syphilis, unclassed	?	7	(A) Wife: none of early syphilis; gumma of soft palate	Negative, except for tertiary lesion	0	0	±	0	Negative	Tertiary syphilis
					(b) Mistress: negative	Negative	0	0	0	0	Negative	Nonsyphilitic
31	Husband	Cerebrospinal syphilis, unclassed	14	13	Negative	Negative, except for hypertension	0	1	±	0	Negative	Nonsyphilitic
37	Husband	Cerebrospinal syphilis, unclassed	27	7	Just after marriage, rash lasting 4 weeks; for 2 years headache, girdle sensation	Anisocoria, eccentric irregular pupils; reflexes hyperactive	0	8	+	0	Negative	Cerebrospinal syphilis, unclassed
39	Husband	Cerebrospinal syphilis, unclassed	6?	3	Alopecia 5 months before; congenital syphilitic child	Negative	0	65	+++	4	Paretic	Asymptomatic neurosyphilis
41	Husband	Cerebrospinal syphilis, unclassed	9	7	Extragenital (lip) 2 years ago; well treated	Negative for neurologic signs	0	5	0	0	Negative	Primary syphilis, treated

11	Wife	Cerebrospinal syphilis, asymptomatic	..	5	Infected 2 years before wife, whose spinal puncture was routine diagnostic measure	Negative	4	6	0	0	Negative	Syphilis (Wassermann)
27	Husband	Cerebrospinal syphilis, meningeal	24	20	Shortly after marriage sore throat, bone pains, malaise lasting 6 months	Pupils irregular, sluggish; reflexes exaggerated	0	3	0	0	Negative	Nonsyphilitic (?)
51	Husband	Cerebrospinal syphilis, meningeal	5	12	Negative; has had a syphilitic child	Negative	1	0	0	0	Negative	Latent syphilis
53	Husband	Cerebrospinal syphilis, unclassed	?	3	Rash 1 year ago	Inequalities of deep reflexes	4	?	+	4	Paretic	Cerebrospinal syphilis, unclassed
54	Husband	Cerebrospinal syphilis, unclassed	?	12	None	Negative	4	0	0	0	Negative	Syphilis (Wassermann)
57	Wife	Cerebrospinal syphilis, unclassed	24	14	None	Negative	0	0	0	0	Negative	Nonsyphilitic
58	Husband	Cerebrospinal syphilis, unclassed	?	15	None of early syphilis	Skin gumma; neurologic examination negative	4	0	0	0	Negative	Tertiary syphilis
59	Wife	Cerebrospinal syphilis, unclassed	6	⅔	None	Roseola	4	0	0	0	Negative	Early secondary syphilis
61	Husband	Cerebrospinal syphilis, unclassed	17	14	None	Negative	4	0	0	0	Negative	Syphilis (Wassermann)
56	Husband	Cerebrospinal syphilis, meningeal	?	7	None	Negative	0	0	0	0	Negative	Nonsyphilitic
68	Husband	Cerebrospinal syphilis, optic atrophy	?	27	None	Reflexes hyperactive	0	18	+++	4	Paretic	Asymptomatic cerebrospinal syphilis
55	Husband	Cerebrospinal syphilis, optic atrophy	?	6	None of early syphilis	Gumma soft palate; neurologic examination negative	4	2	+	4	Paretic	Tertiary and cerebrospinal syphilis, asymptomatic
69	Husband	Cerebrospinal syphilis, meningovascular	12	14	None	Negative	0	0	0	0	Negative	Nonsyphilitic
70	Husband	Cerebrospinal syphilis, unclassed	3	3	Two spontaneous abortions	Negative	0	0	0	0	Negative	Nonsyphilitic (?)
71	Husband	Tertiary syphilis, cerebrospinal fluid negative	12	29	None	Irregular, sluggish pupils	4	4	+	4	Paretic	Cerebrospinal syphilis, unclassed
60	Husband	Syphilis Wassermann; cerebrospinal fluid negative	7	3	None	Roseola; neurologic examination negative	4	7	+	4	Paretic	Secondary and cerebrospinal syphilis, asymptomatic
67	Husband	Syphilis Wassermann; cerebrospinal fluid negative	5	3	None	Roseola; neurologic examination negative	4	8	++	0	Paretic	Secondary and cerebrospinal syphilis, asymptomatic
62	Husband	Syphilis Wassermann; cerebrospinal fluid negative	15	16	None	Irregular pupils; reflexes hyperactive	4	?	++	4	Paretic	Cerebrospinal syphilis, unclassed
121	Husband	Cerebrospinal syphilis, vascular	4	4	Rash for 2 months	Maculopapular syphilid; irregular sluggish pupils	4	3	0	0	Negative	Early secondary syphilis
122	Husband	Cerebrospinal syphilis, unclassed	?	14	Rash for 6 weeks	Maculopapular syphilid	4	?	0	0	Negative	Early secondary syphilis

ners of the parenchymatous group all showed spinal fluids of our Group 3 type (abnormalities usually present in paretic fluids) [3] and are probably to be regarded as candidates for future parenchymatous neurosyphilis. In general, furthermore, the asymptomatic partners of the patients with cerebrospinal syphilis would be classed in our Group 2,[3] which we regard as the serologic precursor of clinical diffuse cerebrospinal syphilis. If these predictions as to future course are correct, then conjugal neurosyphilis of the same type is even more frequent than is indicated by the table. The material is too small to permit any comparisons between the parenchymatous and cerebrospinal groups, although it is our impression, unfortified by figures, that

TABLE 7.—*Summary of Families with Cerebrospinal Syphilis*

	Number of Families	Number of Partners Examined	Number of Partners Normal	Total Number of Partners Syphilitic	Percentage of Partners Syphilitic	Partners Probably or Certainly Neurosyphilitic	Percentage of Syphilitic Partners with Neurosyphilis
Early cerebrospinal syphilis	18	18	3	15	83.6	3	20.0
Late cerebrospinal syphilis	33	34	9	25	73.5	7	28.0
Total	51	52	12	40	76.5	10	25.0

TABLE 8.—*Types of Conjugal Neurosyphilis Observed in 111 Families*

Neurosyphilitic Disease in Person Introducing Syphilis	Number of Instances of Conjugal Neurosyphilis	Type of Neurosyphilis in Partner Probably Similar to That in the One Introducing Syphilis	Neurosyphilis in Partner Dissimilar in Type	Neurosyphilis in Partner Asymptomatic
Parenchymatous (paresis or tabes)	22	8	9	5
Cerebrospinal (early or late)	10	4	2	4

parenchymatous neurosyphilis is more common among the partners of paretic and tabetic persons than among those of persons with cerebrospinal syphilis.

RELATION OF SYPHILIS IN MARITAL PARTNER TO TIME OF MARRIAGE AND DURATION OF INFECTION IN ORIGINAL PARTNER

The data relating to these points are summed up in Table 9. As in our first paper, it is shown that the danger of infection for the partner increases as the date of infection in the one introducing syphilis approaches the year of marriage. The group of families with early cerebrospinal syphilis is purposely omitted, since here recent infection was common in both the person acquiring syphilis and in the marital partner. A point of considerable interest appearing from this material

is that a neurosyphilitic person may be infectious over long periods of time, since of eleven of such patients infected more than five years before marriage, four transmitted the disease to their spouses. Three of these were paretic or tabetic, demonstrating that in these instances, at least, the invading organism had attacked not only the central nervous system, but was also capable of producing lesions elsewhere (skin, mucosa, or testis), thus providing for egress of the organism from the host and propagation of the strain. These instances meet the objection raised by the antagonists of neurotropism, namely, that a strain of organism invading chiefly the nervous system must soon disappear because of its inability to reach the exterior and reproduce itself. It is obvious that in many patients with parenchymatous neurosyphilis other organs than the nervous system may be, and sometimes are, involved.

TABLE 9.—*Duration of Syphilis in Originally Infected Partner in Relation to Time of Marriage and Status of Health of Spouse*

	Status of Wife or Husband								
	Parenchymatous Group			Group with Late Cerebrospinal Syphilis			Total		
Duration of Syphilis in One Introducing Syphilis	Normal	Syphilitic	Percentage Syphilitic	Normal	Syphilitic	Percentage Syphilitic	Normal	Syphilitic	Percentage Syphilitic
More than 10 years before marriage	3	2	40.0	1	1	50.0	4	3	42.8
From 5 to 10 years before	3	1	25.0	..	..	....	3	1	33.3
From 1 to 5 years before	6	8	57.1	2	7	77.7	8	15	65.2
Year of marriage	..	3	100.0	2	2	50.0	2	5	71.4
After marriage	1	5	83.3	2	7	77.7	3	12	80.0
Duration unknown	11	17	62.9	2	8	80.0	13	25	65.7

The average duration of syphilis in the original patient of the paretic group was 16.6 years; in the tabetic, 17.2 years (combined average for the parenchymatous group, 16.9 years); in the late cerebrospinal group, on the contrary, it was 10.6 years. This indicates that in general neurologic symptoms appear some years earlier in diffuse than in parenchymatous neurosyphilis.[4] It also raises the question, however, as to how many of the patients whose disease was diagnosed as cerebrospinal syphilis on admission would have developed tabes or paresis if allowed to go untreated. If the transition from one group to the other is common, our conclusions as to the varying incidence of conjugal neurosyphilis in the two groups are probably at fault. This point cannot be answered definitely; we can only say that in our experience such a transition in the type of neurosyphilitic disease is uncommon.

4. Fournier, A.: Traitement de la syphilis, Paris, Vigot Frères, 1909, p. 442. Fournier has made almost precisely the same observation.

LESIONS OF EARLY SYPHILIS IN THE MARITAL PARTNERS OF PERSONS WITH NEUROSYPHILIS

Prominent among others, Fournier [5] has called attention to the fact that in neurosyphilitic persons, particularly in paretic patients, early lesions of syphilis are often conspicuous by their absence. In our first paper [1] attention was drawn to this point in the partners of neurosyphilitic persons. Complete latency of infection was the rule among the syphilitic partners of parenchymatous neurosyphilitic patients; while of the spouses of patients with cerebrospinal syphilis, two thirds had shown manifestations of the disease outside the nervous system. The material provided by our total, 111 families, summed up in Table 10, shows this striking discrepancy. Of the syphilitic partners of persons with parenchymatous neurosyphilis, less than one third had had obvious lesions of the disease, while among the partners of persons with cerebrospinal syphilis, more than two thirds had had definite

TABLE 10.—*Lesions of Syphilis Other Than Neurosyphilis in Marital Partners of Neurosyphilitic Persons*

Type of Neurosyphilitic Disease in Person Introducing Syphilis	Total Number of Partners Syphilitic	History or Lesions of Syphilis in Partners		Complete Latency of Infection (Except for Neurosyphilis)	Percentage of Syphilitic Partners with Lesions	Percentage of Partners Showing Complete Latency
		Early (Primary or Secondary)	Late (Tertiary)			
Parenchymatous.....	38	9	3	26	31.5	68.5
Early cerebrospinal....	15	11	..	4	73.4	26.6
Late cerebrospinal.....	26	15	3	8	69.3	30.7

early lesions. This difference in the general course of syphilis, together with the other points of variance already mentioned, suggests a quite different pathogenesis for the two main types of neurosyphilitic disease, either due to difference in strain of organism or to similar differences in the defense mechanism of groups of persons.

COMMENT

It is not permissible to draw conclusions as to the probable frequency of conjugal neurosyphilis until a comparison has been instituted between the percentage of incidence of neurosyphilis in the partners of neurosyphilitic persons and in an unselected class of syphilitic patients whose disease is approximately of the same duration. Fortunately, an accurate comparison may be made with unselected material from our own clinic, the details of which have been reported in previous papers.[6] Of the total, 113 partners of our 111 families, nineteen were men and ninety-

5. Fournier, A.: Paralysie générale et syphilis, Paris, Masson et Cie, 1905.
6. Moore, J. E.: Studies in Asymptomatic Neurosyphilis. III. The Apparent Influence of Pregnancy on the Incidence of Neurosyphilis in Women, Arch. Int. Med. **30**:548 (Nov.) 1922. Also Footnote 3.

four women, the male, as usual, being the member to introduce syphilis into the family. The small number of male partners precludes any accurate comparison. The data as to the females, however, are shown in Table 11.

In about 2,500 syphilitic women, whites and negresses, representing all stages of the disease, the incidence of all types of clinical neurosyphilis is 6.47 per cent. As is shown by the table, an additional 18.2 per cent. of women (with early and late syphilis) without definite neurologic signs present definite abnormalities in the cerebrospinal fluid. It may be fairly stated, therefore, that in a large unselected group of women with syphilis, the incidence of neurosyphilis, clinical or asymptomatic, is approximately 25 per cent.

The incidence of neurosyphilis among the wives of men with parenchymatous neurosyphilis is more than twice as great as in the

TABLE 11.—*Actual Incidence of Neurosyphilis Among Wives of Neurosyphilitic Men, Compared with Expected Incidence in an Unselected Group of Women*

Group			Total Number of Women	Number of Women Syphilitic	Number of Women Neurosyphilitic	Percentage Incidence of Neurosyphilis	
Partners of parenchymatous neurosyphilitic persons			52	33	19	57.5	
Partners of cerebrospinal syphilitic persons			42	32	9	28.1	
Unselected Group of Female Syphilitics	Clinical neurosyphilis			2438	158		6.47
	Asymptomatic neurosyphilis	Early syphilis		115	25	22.1	18.2
		Late syphilis		233	38	16.3	
	Total						24.67

unselected group. In the wives of men with cerebrospinal neurosyphilis it is only half that of the parenchymatous group and only slightly greater than in the unselected series. A study of these figures renders it difficult to escape the conclusion that there is a neurotropic strain of *Spirochaeta pallida*, which has a special predilection for nervous tissue, and that this strain of organism tends especially to cause parenchymatous neurosyphilis.

It has been apparent throughout this paper that marked differences exist between the parenchymatous and the cerebrospinal groups. In order to determine whether these differences are found only in our own material or in that of other investigators as well, we have compared our data with those of Plaut and Göring,[7] Schacherl,[8] Raven,[9] and

7. Plaut, F., and Göring, M. H.: Untersuchungen an Kindern und Ehegatten von Paralytikern, München. med. Wchnschr. **58**:1959, 1911.

8. Schacherl, M.: Ueber Luetikerfamilien, Jahr. f. Psychiat. u. Neurol. **36**:521, 1914.

9. Raven, W.: Serologische und Klinische Untersuchungen bei Syphilitiker-familien, Deutsch. Ztschr. f. Nervenh. **51**:342, 1914.

Seelert.[10] It was pointed out in our first paper that the communications from these investigators were the most satisfactory in the literature and that they differed from our own work only in their failure to employ spinal puncture as a routine method of study. This omission certainly results in failure to detect an occasional case of asymptomatic neurosyphilis, so that our own percentages of conjugal neurosyphilis are throughout somewhat higher than those of any of these authors. Unfortunately, no more recent studies from other clinics are available for comparison. In Table 12, however, is shown a comparison of our material with the combined figures of these four writers. The same discrepancies in the two group types of neurosyphilis are evident in

TABLE 12.—*Comparison of Author's Material with That of Four Other Authors*

Type of Neurosyphilis in Person Introducing Syphilis	Reporter	Total Number of Families Examined	Number of Marital Partners Examined	Marital Partner Found to be			Percentage of Syphilitic Partners Who Were Neurosyphilitic
				Normal	Total Number Syphilitic	Certainly or Probably Neurosyphilitic	
Parenchymatous: general paresis or tabes dorsalis	Combined figures of Plaut and Göring, Schacherl, Raven, and Seelert	203	199	72	127	53	41.7
	Combined figures of Moore and Keidel and the present study	65	66	24	42	26	61.9
	Total	268	265	96	169	79	46.7
Nonparenchymatous: Early or late meningovascular neurosyphilis; "Cerebrospinal syphilis"	Combined figures of Schacherl and Raven	27	27	3	24	8	33.3
	Combined figures of Moore and Keidel, and the present study	51	52	12	40	10	25.0
	Total	78	79	15	64	18	28.1

both sets of statistics and in a combination of the two. Neurosyphilis is almost twice as frequent among the partners of tabetic and paretic persons as in the spouses of those with cerebrospinal syphilis.

It is at least strongly indicated by these facts that parenchymatous neurosyphilis is caused by a special strain of *Spirochaeta pallida*, which invades chiefly the nervous system but is also capable of involving such other organs of the body (skin, mucous membranes or male generative apparatus) as may provide for a mode of egress, infection of others and propagation of the strain. It is suggested by a study of some of our families that the infectivity of this hypothetic strain

10. Seelert, H.: Untersuchungen der Familienangehörigen von Paralytikern und Tabikern auf Syphilis, Monatschr. f. Psychiat. u. Neurol. **41**:329, 1917.

is not limited to the first two or three years of the disease, when obvious external lesions are not infrequent, but may extend over a long period of years. In Family 38 (first paper), the wife was infected by her husband, who had acquired syphilis thirteen years prior to marriage; in Family 80, infection in the husband antedated marriage by ten and one-half years. In these instances and in others which have come to our attention, the absence of demonstrable infectious lesions or a history of them in the one introducing syphilis leads to the presumption of the probability of seminal infection, although the lack of adequate experimental demonstration of the infectiousness of seminal fluid in late syphilis is recognized as a drawback to this hypothesis.

As for the course of syphilis in the partners of persons with cerebrospinal syphilis, the case is not so clear. The incidence of neurosyphilis is here only slightly higher than in an unselected group of syphilitic patients, the difference in percentages being within the limits of probable error. It is possible that diffuse cerebrospinal syphilis is caused by a second neurotropic strain of organism capable of invading the nervous system, but also prone to involve other organs, particularly at the beginning of the disease. On the other hand, it is more probable that this type of neurosyphilis may be caused by an undifferentiated strain of spirochete capable of producing lesions anywhere in the body.

Although the data submitted in this paper offer some evidence of the possible neurotropism of a strain of *Spirochaeta pallida,* it must not be forgotten that other factors in a given person or family may strongly influence the probability of parenchymatous neurosyphilis. We have offered evidence to show that familial predisposition certainly plays some rôle.[11] The three families reported in our second paper included eight members, all of whom acquired syphilis at different times and from different sources, yet all developed neurosyphilis. Since the publication of this paper, two additional families have come to light among our material. In the first, two brothers, acquiring syphilis from different women, at widely separated dates, have general paresis. In the second family, the father acquired syphilis in 1900 and died in 1918 of paresis; his son contracted the disease in 1919, and in 1923 has typical taboparesis. The fact that in five families such an occurrence has been observed is too striking for mere coincidence. In certain families the nervous system must be considered as a locus minoris resistentae. This point, frequently mentioned by older syphilologists, has apparently been lost sight of in recent years.

11. Moore, J. E., and Keidel, A.: Studies in Familial Neurosyphilis. II. Familial Neurosyphilis from Various Extrafamilial Sources, J. A. M. A. **80**: 818 (March 24) 1923.

The influence of the kind and amount of previous treatment on the incidence of parenchymatous neurosyphilis, so well illustrated by the classical figures of Mattauschek and Pilcz,[12] cannot as yet be evaluated for the arsphenamin era. An interval of many years must elapse before material sufficiently large to be of value can accumulate. With regard to the data of this paper, however, it may be stated that of the syphilitic partners of neurosyphilitic patients, practically none had received any previous treatment; indeed, our examination was usually the first indication that the person had syphilis.

Such other possible etiologic factors as the influence of pregnancy,[13] alcoholism, stress of life and social level are, we think, fairly well controlled in our material. Even if these factors were more largely operative in our series of spouses of neurosyphilitic persons than in our unselected group of women, the differences in the incidence of neurosyphilis in the two groups could not be eliminated.

It seems to us that from the clinical standpoint, at least, the question of neurotropism cannot be solved. The statistics presented in this paper are more complete and more convincing than any heretofore published, and although we feel that further study along these same lines is of great practical value and will probably corroborate our own findings, multiplication of statistics will add little to the solution of the problem. Clinical evidence such as we present can only suggest the existence of a neurotropic strain of spirochete; absolute proof rests on experiment.

Some animal experimentation has been carried out, notably by Noguchi,[14] Reasoner,[15] Plaut and Mulzer,[16] and Levaditi and Marie.[17] The results obtained by the three first named, like our own clinical evidence, are only suggestive. The experiments carried out by Levaditi and Marie are, as we have pointed out,[11] together with Jahnel[18] and Plaut and Mulzer,[16] completely invalidated by the similarity of their neurotropic strain to *Spirochaeta cuniculi*, the organism of spontaneous

12. Mattauschek and Pilcz: Zweite Mitteilung über 4,134 katamnestisch verfolgte Fälle von luetischer Infektion, Ztschr. f. d. ges. Neurol. u. Psychiat. **15**:608, 1913.

13. Moore, J. E.: Studies on the Influence of Pregnancy in Syphilis. I. The Course of Syphilitic Infection in Pregnant Women, Bull. Johns Hopkins Hosp. **34**:89, 1923. Also Footnote 6.

14. Noguchi, H.: Morphological and Pathogenic Variations in Treponema pallidum, J. Exper. Med. **15**:201, 1912.

15. Reasoner, M. A.: Some Phases of Experimental Syphilis with Special Reference to the Question of Strains, J. A. M. A. **67**:1799 (Dec. 16) 1916.

16. Plaut, F., and Mulzer, P.: Die Liquordiagnostik in Dienste der Experimentellen Kaninchensyphilis, München. med. Wchnschr. **69**:496, 1922.

17. Levaditi, C., and Marie, A.: Etudes sur le treponème de la paralysie générale, Ann. de l'Inst. Pasteur **33**:741, 1919.

18. Jahnel, F.: Das Problem der progressiven Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **76**:166, 1922.

venereal spirochetosis in rabbits. It is possible to solve this problem through experimental syphilis in rabbits, but much more prolonged and careful work than has yet been done is necessary.

SUMMARY AND CONCLUSIONS

1. The complete routine physical, neurologic and serologic examination of 113 marital partners of 111 neurosyphilitic persons are reported.

2. Of the sixty spouses of paretic and tabetic persons, about two-thirds were syphilitic. Of these syphilitic spouses, 57 per cent. were neurosyphilitic.

3. In eighteen families, the entrance of syphilis was of recent date, and one member had early cerebrospinal syphilis (clinical or asymptomatic). Fifteen of the eighteen partners had also recently acquired the infection; but, although presumably infected by the same strain causing neurosyphilis in the original member, only three of these were neurosyphilitic.

4. Among the marital partners of patients with late cerebrospinal syphilis, the incidence of syphilis was high, but that of neurosyphilis in the syphilitic partners was low (28 per cent.).

5. Conjugal neurosyphilis was observed in thirty-two instances, in nine of these being detected only because of the routine use of cerebrospinal fluid examination. Conjugal neurosyphilis of the same general clinical type was comparatively frequent.

6. Although the danger of infection for the spouse increases as the date of infection in the one acquiring syphilis approaches the year of marriage, it is shown that neurosyphilitic patients may be infectious for many years, in spite of the absence of demonstrable open lesions.

7. In two thirds of the syphilitic partners of persons with parenchymatous neurosyphilis, the course of syphilitic infection had been completely latent; while among the partners of cerebrospinal neurosyphilitic persons, more than two thirds had had outspoken early or late lesions of the disease.

8. It is shown by our own material and by the data of other investigators that the incidence of neurosyphilis among the partners of persons with parenchymatous neurosyphilis is more than twice as great as in a large unselected group of women, although in the partners of persons with cerebrospinal syphilis, neurosyphilis is no more frequent than in the unselected group.

9. These data offer suggestive evidence of the existence of a neurotropic strain of *Spirochaeta pallida* as an etiologic factor in neurosyphilis of the parenchymatous type. This hypothesis does not apply to diffuse cerebrospinal syphilis, in which case evidence supporting the theory of special strain is lacking.

10. It is pointed out that other factors than strain, such as familial predisposition, treatment, pregnancy and other conditions may be operative in the etiology of neurosyphilis.

11. Although the clinical evidence in favor of neurotropism offered by this paper is suggestive, it must be confirmed by adequate laboratory investigations, which are not yet available.

12. The practical value of this work is self-evident. Every marital partner of a neurosyphilitic patient is himself potentially neurosyphilitic. Routine examination of the spouse by all available means, including especially study of the cerebrospinal fluid, is essential.